The American Journal of DIGESTIVE DISEASES

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DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

Volume 19 — October, 1952 — Number 10

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*Peptic Ulcer. A. C. Ivy, M. I. Grossman and W. H. Bachrach, Blakiston Publishing Co., Phila., 1950.

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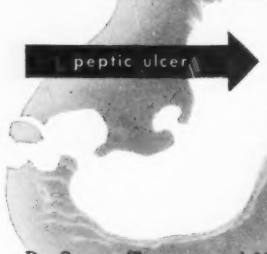
*S. Krasnow, F. Steigmann and L. L. Hardt, Comparison of Effectiveness of Various Antacids on Gastric Acidity. Am. J. Dig. Dis., 17:242 (1950).



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*P. J. Raimondi, Treatment of Duodenal Ulcers with Desiccated, Defatted Duodenal Powder. Permanente Foundation Med. Bull., 8:4 (October), 1950.

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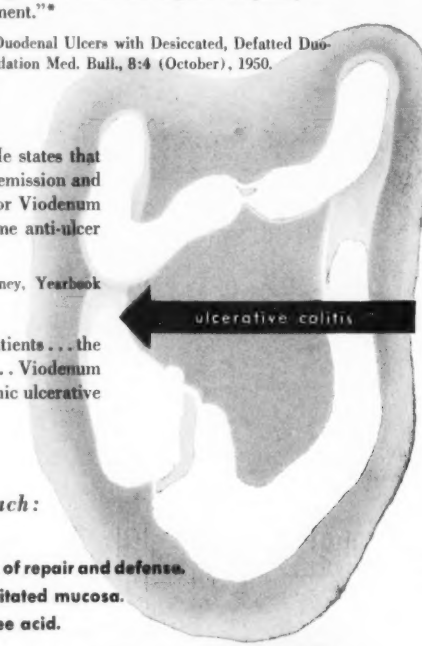
*Medical Management of Gastrointestinal Disorders. Garnett Cheney, Yearbook Publishers, 1950.



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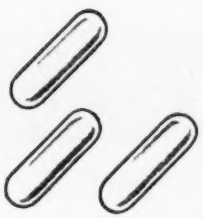

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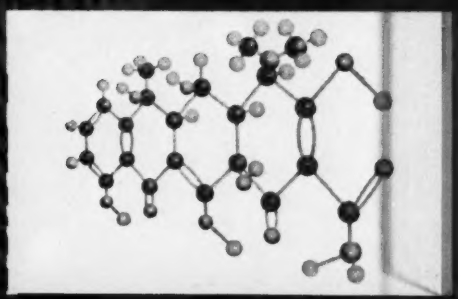

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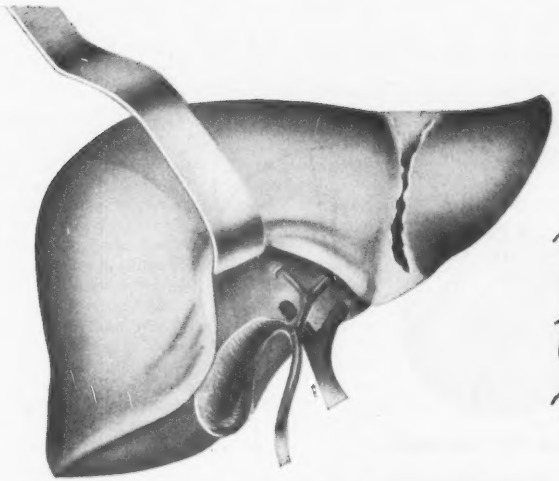

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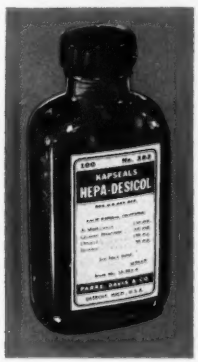

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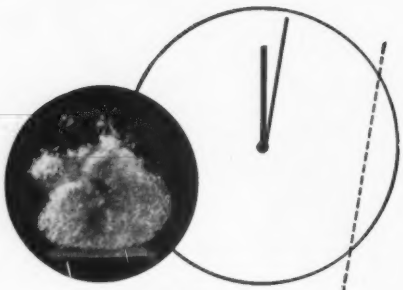

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PHYSICAL EXAMINATION OF THE ESOPHAGUS

EDDY D. PALMER, LT. COL., M. C., Washington, D. C.

IT IS PROBABLY fair to state that no organ of the body is so thoroughly neglected during physical examination as is the esophagus. The esophagus discourages the examiner by its seeming inaccessibility, and the clinician may feel it necessary to pass the entire responsibility for its evaluation on to others. The diagnostic effectiveness of complementary roentgenologic and endoscopic methods is of such a high order that the clinician must necessarily feel relatively impotent when this organ is under consideration. The fallacy of such an attitude on the clinician's part, however, is apparent: the radiologist and endoscopist will not have the opportunity to evaluate the organ unless the physician becomes suspicious of abnormality here. If one reflects on the problem of esophageal carcinoma, he will agree that the information to be gained from the patient's history is usually not nearly revealing enough to encourage a search for an early and perhaps curable lesion. Carcinoma of this organ is one of the most distressing diseases because symptomatic manifestations so often lag behind extra-esophageal extension. Simple routine physical examination of the asymptomatic patient with esophageal cancer, however, may raise enough suspicion of esophageal disease to permit radiologist and endoscopist to make an early diagnosis.

TECHNIC OF EXAMINATION

The esophagus is examined by the ancient method of auscultating the swallowing sounds and timing the interval between initiation of deglutition and emptying of the esophageal ampulla. This is a measure, then, of the swallowing time, and it permits detection of an isolated lesion or diffuse disease which either obstructs flow through the esophagus or interferes with normal esophageal motility. The patient, in the upright position, takes a large swallow of luke-warm water, and the start of the swallow is timed from the moment the larynx makes its sudden upward excursion. This is an easily recognized and physiologically precise point of reference. A stop-watch simplifies the procedure but is not at all necessary for an accurate determination.

The end-point is found by auscultating over the xiphoid and noting the beginning of each esophageal sound. The sounds are heard as distinct gurglings, close to the ear. They begin suddenly and are easily timed. Their duration is of no diagnostic importance and bears no relationship to the amount imbibed. Every swallow is by no means productive of sounds, even though the esophagus be normal.

When a liquid is swallowed, as in this examination, two sounds may result. One, which is heard only upon occasion, immediately follows the buccopharyngeal phase, if the patient is in the upright position. A second, which rather regularly occurs, normally is heard four to seven seconds after the larynx rises, and persists two or three seconds. It is important that the subject's chest remain at rest in partial expiration during this period, so that diaphragmatic action does not lead to passive ampullary emptying. Meltzer's (1) descriptive terms, "Durchspritzgeräusch" and "Durchpressgeräusch," for the first and second sounds, respectively, have been retained in the literature through the many years which have followed his monumental studies on deglutition.

From the Gastrointestinal Section, Walter Reed Army Hospital, Washington, D. C.

Submitted April 11, 1952.

NORMAL MECHANISMS

The sounds are made by the trickling or squirting (2) of an air-liquid mixture from the esophageal ampulla through a narrow orifice into the stomach. If no air is taken in during the course of normal swallowing, no noise will be produced. When liquids are swallowed, they are thrown quickly down to the ampulla by contraction of the mylohyoid muscles (3). Some may penetrate the cardia within a second, producing in an occasional instance the first sound. But most of the liquid is retained in the ampulla (4, 5). The ampulla does not empty itself by its own automatism; rather, it must wait for the primary wave of esophageal peristalsis, which was initiated at the outset of the buccopharyngeal phase, to reach it. The process terminates with ampullary systole, the squirting of detained material into the stomach, and then the second sound. The entire course of events requires from four to seven seconds in the normal adult. It is interrupted by normal respiratory activity of the diaphragm, for the distal esophagus becomes occluded during inspiration and encouraged to dilate during expiration (6). The character and intervals of the sounds change considerably when the subject is in the horizontal position. Similarly, cold fluids tend to be held up for unpredictable periods at the cardia. There appear to be minor variations in the results when fluid materials other than water are used for the test; for convenience as well as standardization, water at approximately body temperature proves to be the best test material. Solid boli behave quite differently from liquids.

CLINICAL USEFULNESS

As with all examination methods, the clinician must be prepared for both falsely positive and falsely negative results when examining the esophagus. Unfortunately, no large-scale studies of the technic's accuracy in detecting the presence of disease have been made. Considerable personal experience permits certain cautious generalizations. There is nothing specific about positive findings—they indicate to the examiner only the presence of an abnormal process, diffuse or localized, which either actually obstructs the lumen or merely interferes with the progress of the organ's primary peristaltic wave. But what the test lacks in specificity it more than makes up in its inclusiveness. This is its particular value.

All of the diffuse intramural esophageal diseases may affect the swallowing time. In scleroderma, mural involvement may preclude coordinate peristaltic activity, so that the affected ampulla empties by gravity rather than by systolic compression. The chronic fibrotic types of esophagitis behave in the same way. The effects of the acute and subacute endogenous esophagitides, on

the other hand, are unpredictable. Sometimes there is no abnormality. At others, the sounds never appear or are delayed, presumably because irritation by the surface lesion leads to peristaltic incoordination and momentary segmental spasm.

The technic is particularly useful in the commonly encountered problem of suspected ingestion of a noxious agent—either liquid corrosive or small solid foreign body. The former possibility, especially, cannot be studied with optimum accuracy if the clinician must inflict on the patient the expense and inconvenience of serial roentgenographic and endoscopic examinations. Initial studies suggesting absence of immediate corrosive damage cannot be accepted as assurance that the possibility of later stenotic changes has passed. The simple technic of periodic evaluation of swallowing function, after the radiologist and esophagoscopist have reported absence of injury, may supply adequate warning of trouble during the patient's dangerous asymptomatic period. Similar useful application can be made when a patient reports that he believes a fish-bone has become lodged in his gullet. Here, after the physician has obtained—without enthusiasm or confidence—negative x-ray studies, he may hesitate to recommend immediate esophagoscopic examination. At such times, inability to demonstrate normal swallowing sounds should be considered an urgent indication for further study. Normal sounds, on the other hand, have been found to justify confidence in a clinical impression of absent foreign body.

Small isolated lesions do not influence the sounds in an entirely predictable way, but in general a change seems to depend on two features: their ability to act as points of irritation, leading to muscular incoordination or spasm, and their simple physical interference with muscular activity through intramural extension. Thus, peptic ulcers and strictures of the esophagus characteristically either entirely prevent the appearance of the sounds or cause excessive prolongation of the swallowing interval. Occasionally mid-thoracic and epiphrenic diverticula may do the same, but these lesions produce no reliable changes. Experience with polyps and benign intramural tumors has been sparse, but it appears that the former do not and the latter may interfere with the sounds. Esophageal varices and extrinsic pressure phenomena have no effect.

Fortunately, the important problem, that of early diagnosis of esophageal carcinoma, can effectively be approached through study of the swallowing sounds. Most malignant lesions of the distal half of the organ already have produced a change in the sounds by the time they become detectable by the common diagnostic methods. Most of those involving the proximal half, it appears, exert an effect only after attaining relatively large sizes, but this has often been found to antedate the onset of symptoms. Routine study of the swallowing sounds can be expected to raise enough question of disease in most cases of early carcinoma to permit detection of a significant portion of asymptomatic lesions.

SUMMARY

Physical examination of the esophagus is easily and quickly accomplished, and gives information which is invaluable in routine screening for esophageal disease. It is an ancient technic which has been neglected in spite of the fact that it offers a simple and rather effective means for detecting carcinoma during the prepatent and curable stage.

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ANTACIDS: FACT AND FANCY

F. STEIGMANN, M. D., L. L. HARDT, M. D. AND S. HYMAN, M. D., Chicago, Ill.

INTRODUCTION

THE MAGNITUDE of the peptic ulcer problem among the population and the presently accepted method of treatment of over 90 per cent of such patients by medical management is a constant stimulus to develop effective measures for control. Fundamentally, this quest resolves itself into the discovery of a substance which will effectively decrease or completely eliminate free acid in the stomach of such patients.

Physicians, and the public too, are constantly besieged by drug salesmen, literature and other channels of advertising, relative to the efficacy of numerous products, which, allegedly, will relieve peptic ulcer symptoms. The frequent lack of correlation of clinical results with the enthusiastic and extravagant claims in advertising, indicates the need for more controlled studies of such products. We wish, therefore, to present the results of testing for their antacid properties a number of commonly used and advertised drugs and remedies for relief of ulcer symptoms.

The various procedures for estimating the efficiency of antacid drugs are limited by lack of complete knowledge of the mechanism of gastric secretion. Animal experiments, though helpful, are not directly applicable to man because of species differences in physiologic and pharmacologic response. The normal man is not entirely suitable as a test subject since his output of acid is less than that of patients with duodenal ulcer.

From the Departments of Therapeutics and Internal Medicine, Cook County Hospital; the Department of Internal Medicine, College of Medicine, University of Illinois and the Department of Internal Medicine, Loyola University Stritch School of Medicine, Chicago, Illinois.

Aided by a grant from the Hardt Foundation.

Submitted April 2, 1952.

TABLE I

ALKALI SUBSTANCES

Difference in free acidity measured at fifteen minute intervals, when Histamine alone and Histamine plus an Alkali Substance was administered.

Chemical Composition	Trade Name	Dose	No. of Cases	Time in Minutes 15	30	45	60	75
Magnesium Hydroxide - 0.5 Gm. Calcium Carbonate 10 grains Sodium Bicarbonate 10 grains	MAG-OH (39-80A)	2 Tab.	5	-22	-16	-19	-6	10
	SIPPY No. 1	2 Tab.	8	-31	-45	-33	-23	-18

Antacid efficiency, therefore, must be determined directly in patients with gastro-duodenal ulcer, and under well-controlled conditions. Indeed, even under such circumstances, the results may be complicated by physiological stimuli during test periods, inhibitory as well as stimulatory, which occasionally significantly influence the gastric response to drugs at a given time. Moreover, natural fluctuations in gastric secretion in man are great and frequent and may influence experimental results (1).

Evaluations of antacid properties of drugs based upon subjective relief of symptoms (2), rate of healing of the ulcer crater as measured roentgenographically (3, 4, 5) and the rate of recurrence of ulcer symptoms (6, 7, 8) have been reported and found to be not entirely satisfactory.

The primary consideration in the evaluation of antacid drugs for clinical application is their effect upon the gastric contents of ulcer patients, for the goal of therapy with such drugs is the effective neutralization or inhibition of the free acid (9, 10) and consequently of the peptic activity of the gastric secretion (11).

TABLE II

CELLULOSE COMPOUNDS

Difference in free acidity measured at fifteen minute intervals when Histamine alone and Histamine plus a Cellulose Compound was administered.

Chemical Composition	Trade Name	Dose	No. of Cases	Time in Minutes 15	30	45	60	75
Sodium-carboxy-methyl-cellulose 225 mgm. Methyl-cellulose Calcium Carbonate Elm Bark Saccharin Vegetable Flavoring	CARMETHOSE ULMETS	2 Tab.	5	-10	-4	-25	-37	-12
				-48	-22	-8	-2	+7
Sodium-carboxy-methyl-cellulose 225 mgm. Magnesium Oxide 75 mgm.	CARMETHOSE with MAGNESIUM OXIDE	2 Tab.	6	-26	-39	-21	-35	-17

TABLE III

ALUMINUM HYDROXIDE GELS

Difference in free acidity measured at fifteen minute intervals, when Histamine alone and Histamine Plus an aluminum hydoxide gel was administered.

Chemical Composition	Trade Name	Dose	No. of Cases	Time in Minutes 15	30	45	60	75
Aluminum Hydroxide	ALKA-JEL	4 Tab.	7	-15	-12	-5	-5	+35
Aluminum Hydroxide .065 Gram	AMPHO-JEL	2 Tab.	23	-21	-24	-25	-21	-2
Sodium Aluminum Silicate - 1 Gram	LUDO-ZAN	2 Tab.	5	-45	-27	-16	+5	+14

METHODS AND MATERIAL

Our method of testing the antacid drugs consisted of comparing the degree of gastric acidity obtained following histamine injection alone, with that obtained following histamine injection plus the ingestion of the antacid to be tested. Fasting subjects—gastric or duodenal ulcer patients—were intubated with a Levine tube and their gastric contents were completely evacuated. Thereafter, they were aspirated at 15 minute intervals until three additional samples were obtained. After the fourth sample was obtained, the subjects were given 0.1 mgm. of histamine per 10 kilo weight, and the aspirations were continued every 15 minutes for another 75 minutes. On the next day, this technique was repeated. However, at this time, the subjects were given an antacid by mouth simultaneously with the histamine injection. Aspirations were continued as on the previous days.

Twelve groups of antacids, comprising 37 drugs were studied:

1) Alkali substances—Magnesium hydroxide and Sippy No. 1.

2) Cellulose Compounds—Carmethose, Carmethose with magnesium oxide and Ulmets.

3) Colloidal aluminum hydroxide gels—Alkajel, Amphojel, and Ludozan.

4) Alkali combined with anti-secretory substances—magnesium hydroxide with Homatropine, and Bunesia.

5) Amino acid combinations—Aciban, Titrilac, Alminate, Aspogen, and Barbonate.

6) Plant mucin—Okra and Okra plus gastric mucin.

7) Tissue extracts—Viobin and Enterogastrone.

8) Anticholinergics—Banthine.

9) Proprietaries—Tums, Jests and Chooz.

10) Resinous substances—Resinat, Polyamine Methylene, Resin with mucin, Amberlite IR-4, and Resmicon.

11) Colloidal aluminum hydroxide gel combinations with magnesium trisilicate, Hypercin, Pink Alkajel, Tri-creamalate, AMT, Gelusil and Mucotin.

12) A combination of colloidal aluminum hydroxide, magnesium tri-silicate, gastric mucin and a detergent (Sodium Alkyl Sulfate).

TABLE IV

ALKALI AND ANTI-SECRETORY COMBINATIONS

Difference in free acidity measured at 15 minute intervals when Histamine alone and Histamine plus an alkali and anti-secretory combination was administered.

Chemical Composition	Trade Name	Dose	No. of Cases	Time in Minutes 15	30	45	60	75
Magnesium Hydroxide, 0.3 Gm. Homatropine Methyl Bromide 2.5 Gm.	Magnesium Hydroxide with Homatropine (39-80B)	2 Tab.	5	-23	-28	-23	+9	-15
Homatropine 2.5 mgm. Butisol Sodium 10 mgm. Magnesium Hydroxide 300 mgm.	Bunesia	2 Tab.	10	-26	-24	-1	-1	-3

The duration and degree of the antacid effect of these drugs and the presence or absence of acid rebound were studied. The results were tabulated in such a manner as to give only the difference in the values of free acid between the days when histamine alone and histamine plus the antacid were given. Thus, if 15 minutes after the histamine injection, the free acid rose to 80 and the following day after histamine and the particular antacid, it rose only to 50, a minus thirty (-30) was recorded in the table. In a number of patients, the clinical effects of prolonged use of some of these antacids were also observed.

The last three groups named above, resinous substances, colloidal aluminum hydroxide gel combinations with trisilicate and the detergent combination have been more extensively studied and are the subject of separate publications (12, 13, 14, 15).

RESULTS

Of the purely alkali substances, Magnesium Hydroxide and Sippy No. 1 powders, two tablets of the latter showed the greatest and longest action. Each of these drugs, however, had an excellent acid neutralizing power. Both substances had a slight rebound after 60 minutes (Table I).

The cellulose substances showed, in general, a definite and prolonged antacid effect. Ulmets and Carmethose plus Magnesium Oxide showed a marked acid neutralizing ability, while Carmethose alone was only moderately effective. Ulmets had an acid rebound at the end of 60 minutes (Table II).

Of the colloidal aluminum gels, such as alkajel, amphojel and ludozan, the latter had a more marked but short, and amphojel, a moderate and prolonged antacid effect. Alkajel, while having some initial antacid effect, had a marked rebound after 60 minutes, as did also ludozan (Table III).

Combinations of alkali with anti-secretory substances, seemed to have slightly greater antacid effects. The two alkali antispasmodic combinations, magnesium hydroxide with Homatropine and Bunesia had a moderate antacid effect with moderate rebound after 45 minutes (Table IV).

Amino acid combinations, such as Alminate, Aspogen, Aciban and Titrilac, had a significant and prolonged antacid effect in the order named. Barbonate, a combination of Alminate, Phenobarbital and Belladonna had a very minor antacid effect (Table V).

Plant mucin produced a marked and prolonged antacid effect. The addition of animal mucin markedly increased this effect in the few cases studied (Table VI).

Tissue extracts such as Viobin (Duodenal mucosa extract) had a marked but short antacid effect, while enterogastrone given orally had no effect (Table VII).

Banthine alone, had no antacid effect (Table VIII).

Three proprietary substances—Tums, Chooz and Jests—had a marked and prolonged antacid effect in the order named. The latter two, however, (Chooz and Jests) had a marked rebound after 45 and 60 minutes respectively (Table IX).

Since many antacid tablets are flavored with an aromatic oil—a commonly used flavoring agent—peppermint in the form of Life Savers was tested on three patients. This substance had no increasing or decreasing acid effect.

DISCUSSION

This study confirms the previously reported observations by Kirsner and Palmer (16) that alkali and particularly calcium carbonate are useful substances in the treatment of peptic ulcer, because they neutralize acid very efficiently. Calcium carbonate and other alkali, however, have more or less disagreeable side ef-

TABLE V

AMINO ACID COMBINATIONS

Difference in free acidity measured at fifteen minute intervals when Histamine alone and Histamine plus an amino acid combination was administered.

Chemical Composition	Trade Name	Dose	No. of Cases	Time in Minutes 15	30	45	60	75
Calcium Caseinate 0.4 Gm. Calcium Carbonate 0.1 Gm.	ACIBAN	2 Tab.	14	-32	+2	-19	-20	-3
Glycine 0.15 Gm. Calcium Carbonate 0.35 Gm.	TITRALAC	2 Tab.	4	+6	+9	+10	+9	+9
Aluminum Dihydroxy-Amino acetate (Aluminum 18.3% salt of amino acid glycine)	ALMINATE	2 Tab.	8	-37	-26	-20	-5	+2
Basic Aluminum Amino-Acetate 0.5 Gm.	ASPOGEN	2 Tab.	24	-29	-11	-22	-5	+5
Alminate 0.5 mgm. Phenobarbital 8 mgm. Belladonna Alkaloids 16 mgm.	BARBONATE	2 Tab.	7	-14	-12	0	-11	+3

TABLE VI

PLANT MUCIN

Difference in free acidity measured at fifteen minute intervals, when Histamine alone and Histamine plus various Mucins was administered.

Chemical Composition	Trade Name	Dose	No. of Cases	Time in Minutes 15	30	45	60	75
Plant mucin	OKRA	2 Tab.	12	-22	-28	-25	-23	-7
Plant mucin and Gastric Mucin	OKRA + MUCIN	2 Tab.	3	-49	-38	-24	-19	-9

TABLE VII

TISSUE (INTESTINAL MUCOSAL) EXTRACT

Difference in free acidity measured in fifteen minute intervals, when Histamine alone and Histamine and a tissue extract substance was administered.

Chemical Composition	Trade Name	Dose	No. of Cases	Time in Minutes 15	30	45	60	75
Tissue Extract	VIOBIN	2 Teasp.	10	-34	-28	-9	+5	0
Tissue Extract	ENTERO-GAS-TRONE	5 Tab.	11	+4	-1	0	-1	-1

fects—constipation from too much calcium or bismuth; diarrhea from too much magnesium; alkalosis, especially after large doses and prolonged intake of soda bicarbonate (17, 18); renal stones (19, 20); and acid rebound (21, 22, 23). It is obvious, therefore, that in some patients, other substances merit a trial in the medicinal management of peptic ulcer.

Most of the substances introduced during the past thirty years for the treatment of peptic ulcer have some therapeutic usefulness. Thus, it may be stated that the advent of the colloidal aluminum hydroxide preparations (24, 25, 26, 27, 28, 29) has made the prolonged ingestion of medications for peptic ulcer less troublesome for many patients. Nevertheless, these products, too, have some side effects—particularly constipation—which lead patients to discontinue them after a trial of variable length. The addition of magnesium trisilicate (30, 31, 32, 33), which, in itself, is not a strong alkali, but which has a mildly laxative effect—to the colloidal aluminum substances has resulted, in our experience, in a slightly better product for prolonged use.

While the colloidal aluminum products were supposed to have some demulcent effect on irritated gastric mucosa, mucilagenous substances themselves would suggest a more marked demulcent effect. This resulted in the introduction of gastric (animal) mucin (34, 35), vegetable mucin (36), carboxymethyl cellulose (37, 38) as therapeutic substances for peptic ulcer patients because of their antacid and demulcent soothing properties. Clinical experiences with some of them indicate, that, in some patients who do not respond to the simpler products, the former may be of value.

Thus, it appeared that the addition of gastric mucin to a mixture of colloidal aluminum hydroxide and magnesium trisilicate (Mucotin) enhanced, somewhat, the antacid effect (14). Similarly, the addition of gastric mucin to resins seemed to enhance their antacid effect (12).

The addition of a detergent to the above mucin mixture did not seem to improve its antacid effects. Thus, the detergent, sodium alkyl sulfate, has not proved, in our experience, a valuable antacid substance either alone (39) or in combination with a mucin mixture (15).

The introduction of substances formed by the combination of either alkali or colloidal aluminum hydroxide with casein or other amino acids, has given to the clinician additional substances with an enhanced antacid effect (40). However, the antacid effect of protein hydrolysates alone is controversial (41, 42, 43, 44).

Improved antacid effects may also be noted from substances which contain one of the various antacids mixed with an anti-secretory substance with or without a sedative. The improved effect is probably due mainly to the antispasmodic substance since it was observed that the supplementary administration of Atropine orally improves the neutralizing effect of alkali (45), while sedatives were found to have no effect on gastric acidity (46). Clinical observations on the use of such mixtures, especially Bunesia*, confirmed the results of the antacid studies, namely, that a combination of an antacid, antispasmodic and sedative may have a better therapeutic effect than either substance alone.

In keeping with the above observation that the alkali are efficient antacids are the findings that three proprietary drugs—Tums, Chooz and Jests—are combinations of alkali and magnesium trisilicate. While it is true that these substances give very good immediate antacid results, they also create a marked rebound acidity within 45 to 60 minutes.

While not antacids, tissue extracts, viobin and enterogastrone have been suggested for the therapy of

*Twenty-four patients with gastro-duodenal ulceration were studied clinically for the therapeutic effect of Bunesia. All of these patients were cases of recurrent ulcer symptoms and responded well to this substance as a replacement to Tr Belladonna, phenobarbital and the particular antacid they had used. Many felt that they preferred this medication to the previous ones because of its therapeutic effect and its "unity" and all the medication being in one dose. Several patients complained at times about the taste of these tablets, however, but only three stopped this medication because of the taste.

TABLE VIII

ANTICHOLINERGIC SUBSTANCE

Difference in free acidity measured at 15 minute intervals when Histamine alone and Histamine plus an anti-cholinergic substance was administered.

Chemical Composition	Trade Name	Dose	No. of Cases	Time in Minutes 15	30	45	60	75
Methanthaline Bromide 50 mgm.	BANTHINE	2 Tab.	9	-3	+3	+7	+4	-10

TABLE IX

MISCELLANEOUS PROPRIETARIES

Difference in free acidity measured at fifteen minute intervals, when Histamine alone and Histamine plus a proprietary substance was administered.

Chemical Composition	Trade Name	Dose	No. of Cases	Time in Minutes 15	30	45	60	75
Calcium carbonate Magnesium carbonate Magnesium trisilicate Peppermint and sugar	TUMS	2 Tab.	4	-59	-75	-65	-30	+4
Calcium carbonate Magnesium carbonate Magnesium trisilicate	JESTS	2 Tab.	4	-58	-41	-17	+3	+21
Calcium carbonate Magnesium trisilicate Oil of peppermint	CHOOZ	2 Tab.	4	-36	-9	-9	+38	-1

gastro-duodenal ulceration on the basis of "protection" of the stomach wall (47, 48, 49, 50, 51, 52, 53). The latter property remains, yet, to be confirmed by more studies. The antacid effect is definitely short and little, and the use of these substances as antacids for the relief of ulcer pains, must, at present, be questioned.

The absence of any significant antacid effect by the quaternary amine Banthine on the histamine stimulated stomach in confirmation with other observations (45, 54) suggests that relief of pain in ulcer patients taking this substance is probably not on an antacid basis. It is, however, possible that while Banthine does not decrease the acidity in the acute experiments, it may lead to a lower gastric acidity if it is taken for a longer period of time. Kirsner, et al, however, failed to find changes in the response to histamine in a group of patients treated for months with 200-300 mg. of Banthine by mouth daily (45).

The results obtained from the antacid study of the above compounds and from the clinical observations with some of them, it appears logical to conclude that none of them is a panacea for the ulcer patient. Most of them may have some beneficial effect upon the individual who uses them. It seems to indicate, moreover, that the clinician should not fit the patient into his pet regimen, but that the regimen should be built around the patient including diet, medication and environmental changes. This type of treatment should keep the patient more satisfied for a longer time and may prevent the occurrence of so-called "intractable ulcers" due to insufficient and short treatment, as pointed out by Althausen (55).

Some patients will lose their epigastric distress on diet alone, and others when on a vacation. The majority of patients, however, will need some type of an antacid. If calcium carbonate or some other alkali mixture is efficacious in controlling the patient's symptoms and agrees with him, such should be given priority. If not, the clinician may choose from a great number of other antacids, a compound which may be more palatable and more agreeable to the patient. For psychological reasons, the latter compound may frequently be even a better antacid for that particular patient.

Favorable results with a particular antacid should be considered as an individual response of a patient based on many factors. It does not constitute prima facie evidence of superiority of this particular antacid over the others. While some compounds are somewhat superior to others from a laboratory viewpoint, good clinical results are often obtained with both types depending on the variable responses by different patients to the same drug.

While the availability of many antacids is often confusing, it is certainly not a calamity, inasmuch as the discriminating clinician is thus given the opportunity to select for his patient the substance which would best suit his patient.

The ideal antacid has not yet been discovered. There still exists the need for continued research for the development of such a substance.

SUMMARY AND CONCLUSION

The decrease in free acidity in the histamine stimulated stomach has been studied using 37 currently widely used compounds as the test substances.

The results of our observations seem to indicate that the majority of these substances have an antacid effect in variable degrees and for different lengths of time.

Clinical observations in association with the antacid studies indicate that some substances are better tolerated than others and thus produce, at times, better therapeutic results despite the fact that they do not lead to complete neutralization of the gastric acidity in the laboratory.

It is a fancy to consider some antacids greatly superior to others. The fact remains that most of them find, at times, a useful place in the therapy of ulcer patients.

The ideal antacid has not been found. Continued search for such a substance is still indicated.

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MANAGEMENT OF DIABETIC PATIENTS DURING AN ACUTE INFECTION

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THE FACT that, generally speaking, infection aggravates a diabetic condition is well known. Although there are occasional exceptions to this rule, it must be remembered that the most likely probability is an exacerbation of diabetic symptoms during the infection, with the possibility of a permanent deterioration in insulinogenic function after the infection has subsided. This means, from the therapeutic standpoint, that the requirement of the patient for exogenous insulin is greatly increased during the acute disease, and that this requirement must be met by an adjustment of dosage if permanent damage is to be prevented. The ideal medical goal is that the patient shall require no more insulin after the infection for adequate control of the diabetic condition than he did before its onset. When this result is achieved, it is evidence that protective treatment during the infection was adequate to prevent progression of the diabetic state.

Here, as in other phases of the treatment of diabetic patients, the problem must be individualized to meet the needs of the particular patient, since there is much individual variation in the response of the organism already affected by impairment of pancreatic function, to the strain imposed by infection. The severity of the reaction to infection, in some cases at least, evidently is not conditioned entirely by the severity of the diabetic state. Perhaps the best way to comprehend the diversity of the problem is to examine the actual course of events in a group of diabetic patients.

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The first two cases illustrate exceptional instances in which acute infection did *not* result in any aggravation of the diabetic state.

Case 1.—A man, aged 55 years, had a prediabetic condition, according to the glucose tolerance curve,* when I first saw him in April, 1924. At that time he gave the following history: Six months earlier the level of the blood sugar had been 400 mg per cent, and it remained high for three months, never falling below 200 mg per cent on a dosage of 60 units of insulin (40 units in the morning, 20 in the evening). One brother and one sister also had diabetes. The patient reported that during the last six months, he had lost 30 per cent of his weight.

At my first examination, there was only a slight elevation of the blood sugar. The first day I administered 28 units of insulin, then reduced the dose to 20 units on the next three days, and to 5 units on the following day. After that, all insulin was discontinued. His fasting blood sugar was normal during the month of April. In May, a carbuncle developed on his neck and shoulders; the usual expectation would be that

*All glucose tolerance curves represent estimations of the blood sugar just before ingestion of 100 grams of glucose (in water) on a fasting stomach, unless otherwise indicated, and ½, 1, 2, 3 and 4 hours afterward.

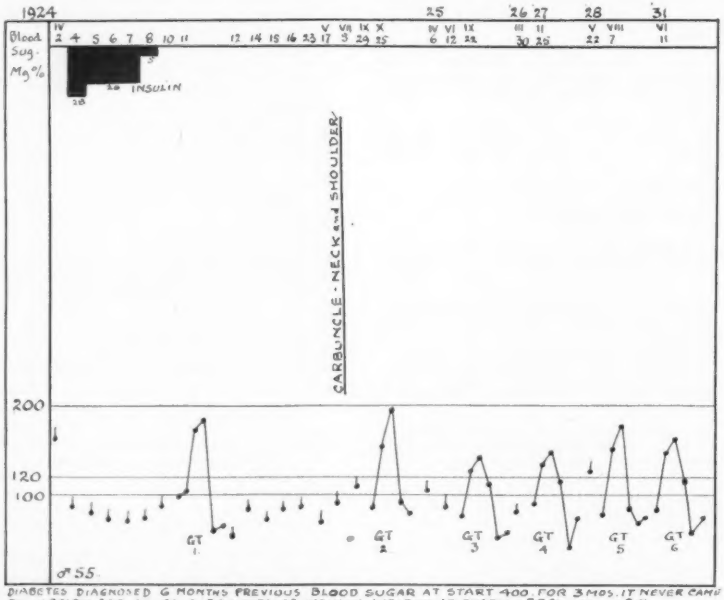

Figure 1.

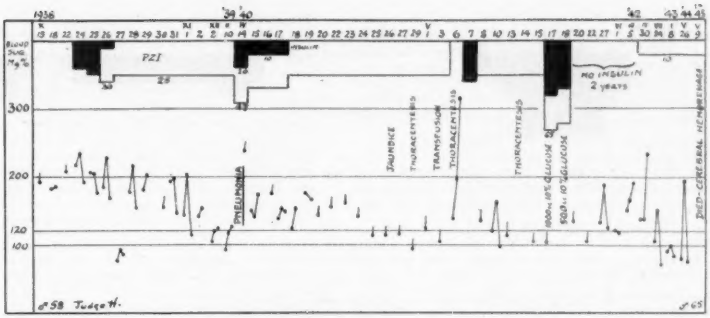

Figure 2.

such a severe infection would upset the diabetic state. As the chart shows (Fig. 1), there was no evidence of disturbance of insulinogenic function, for the level of sugar in the blood remained normal throughout the acute infection. When the glucose tolerance was rechecked five months later, the curve showed no abnormality. Subsequent determinations of the blood sugar and glucose tolerance over a period of seven years were all normal.

Such a picture is unusual. Here was a patient who displayed the classic symptoms of a frank diabetes, and, six months before the record shown on this chart, had had a blood sugar of 400 mg per cent and had required a daily dose of 60 units of insulin for control of the hyperglycemia. This metabolic disturbance subsided, the level of the blood sugar became normal, and even a severe infection did not produce an exacerbation. Within a year, the glucose tolerance curve became normal and remained so for seven years. The only explanation to account for this fortunate course is that the diabetic condition must have been recognized early, before too much permanent damage had been done to the islands of Langerhans, and, since it was treated heroically, as the insulin dosage and the drop of 30 per cent in weight would indicate, the load on the pancreas was lifted and the islands resumed their normal function.

Case 2.—This is another exceptional instance in which an infection did not influence the diabetic condition adversely. The patient was aged 58 years, in 1938, when he was first seen, complaining of a bad toe. Glycosuria and hyperglycemia had been discovered a short time before. Six years earlier, he had been on a special diet in an attempt to lose weight. He had had nocturia, two to three times, for two years, and recently had experienced difficulty in urination. There was no history of diabetes in the family. A general physical examination showed pyorrhea, umbilical hernia, mild hyper-

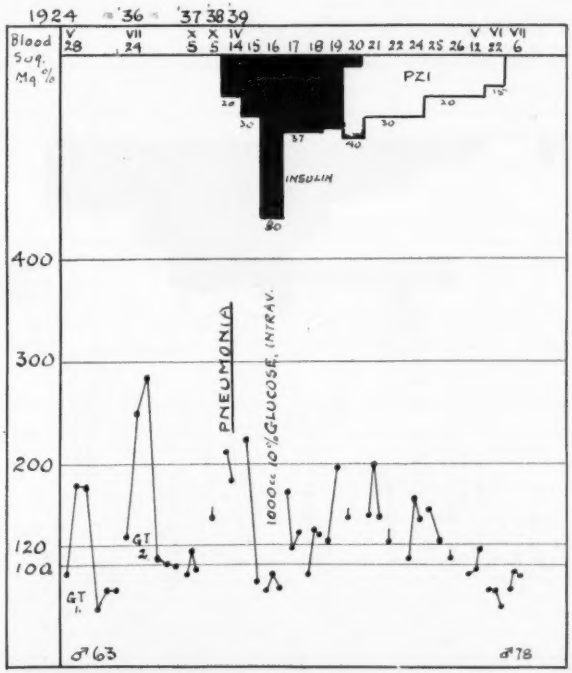

Figure 3.

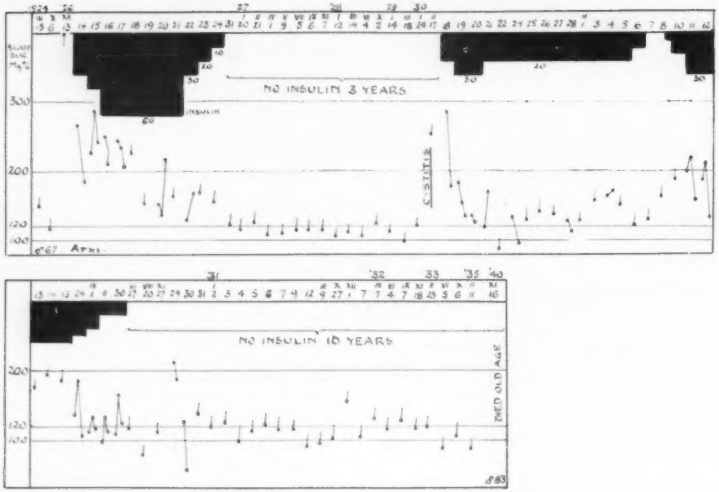

Figure 4.

tension (164 systolic, 90 diastolic), and chronic prostatitis with hypertrophy of the prostate.

When I first saw him in consultation, there was a moderate elevation of the blood sugar. With adequate insulin dosage, this gradually declined to normal in four months, at which time pneumonia developed. Then the situation was further complicated by the appearance of jaundice and pleural effusion for which thoracocentesis had to be performed repeatedly. Transfusions were administered, and the patient had a high fever. With such a severe infection and illness, a considerable disturbance of the carbohydrate metabolism would be expected, but no increase in the dosage of insulin was necessary, and the hyperglycemia remained well controlled. The even more remarkable thing was that toward the end of his hospital stay (May 20, 1940), all insulin was discontinued because of insulin reactions, and for two years afterward he received no insulin. Later the administration of insulin was resumed, but only 10 units daily were required for good control. The patient died in 1945 of a cerebral hemorrhage.

This case is similar to Case 1, that of a diabetic who, at the end of a severe infection, required no insulin for two

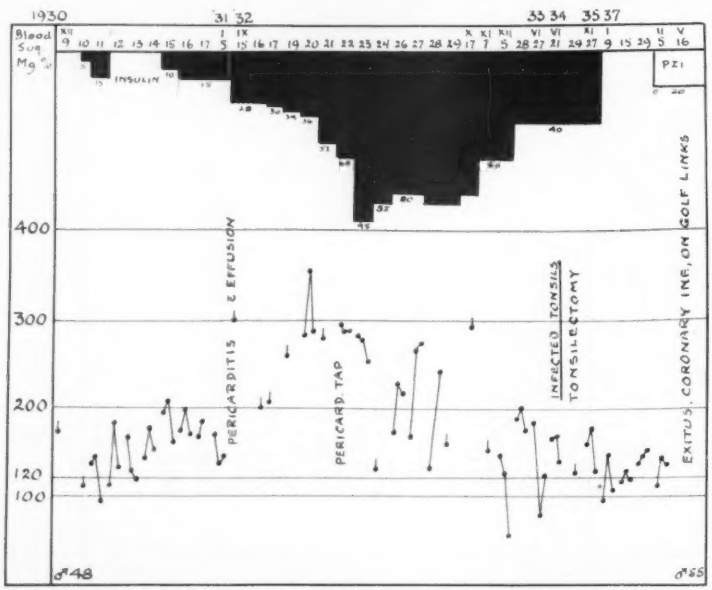

Figure 5.

years, and then took considerably less than had been necessary before the acute illness occurred.

Case 3.—In contrast to the foregoing cases, Figure 3 shows the record of an old man, who was 63 years old when I first saw him. Because of glycosuria, a glucose tolerance test was done, but yielded normal findings. Twelve years later, however, a second glucose tolerance determination, when the patient was taking a normal diet, showed a prediabetic curve, but subsequent checks of the blood sugar three times daily before meals showed no abnormality. In 1938, when he was aged 77 years, the patient had pneumonia which elevated the blood sugar. Insulin was administered for protection, the blood sugar gradually declined and remained normal after all insulin was discontinued at the age of 78 years.

This record shows clearly the effect of a severe infection, even on a mild diabetes. However, when the disturbance is properly counteracted with adequate dosage of insulin during the infection, the patient is protected so that the insulinogenic function does not deteriorate permanently. This patient required no insulin at age 63, when I first saw him, and at age 78, after the subsidence of a hyperglycemia resulting from an acute infection, he was still well without insulin.

Case 4.—In another case (Fig. 4) an old man, who was aged 67 years when diabetes developed, received insulin for ten days and then required no insulin for three years, during which time his blood sugar was normal. Then an attack of cystitis occurred and was accompanied by a pronounced rise in the blood sugar. Administration of insulin had to be resumed and was continued for four months. Then it was discontinued and never was necessary during the ten years until his death at the age of 83 years.

In this old man, the diabetes was extremely mild, but in spite of this, cystitis upset the condition and insulin had to be administered until adequate restitution of the insulinogenic function occurred; subsequently, however, good control was maintained without insulin.

Case 5.—Figure 5 represents a case in a man, who was 48 years of age in 1930 when he became a mild diabetic. Pericarditis with effusion supervened six months later and large doses of insulin were required for several months. Tonsillectomy was performed, because of infected tonsils, in 1934; afterward the diabetic condition improved and the insulin dosage was reduced and eventually discontinued in 1937. A few months later, he died on the golf links, of coronary occlusion.

This is another instance of a patient with mild diabetes which was markedly aggravated when pericarditis developed; the insulin dosage had to be increased up to 95 units a day,

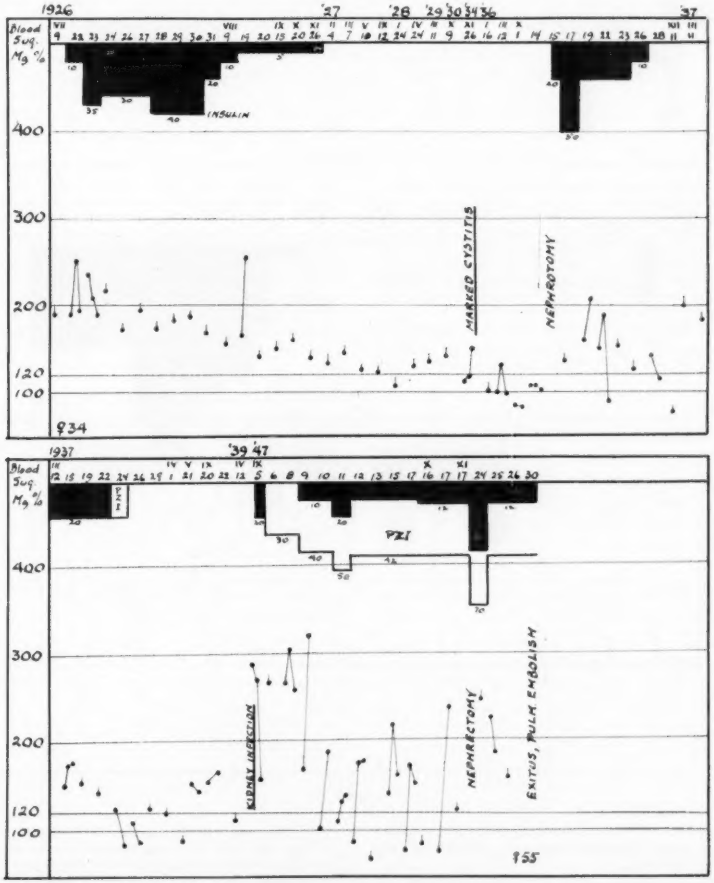

Figure 6.

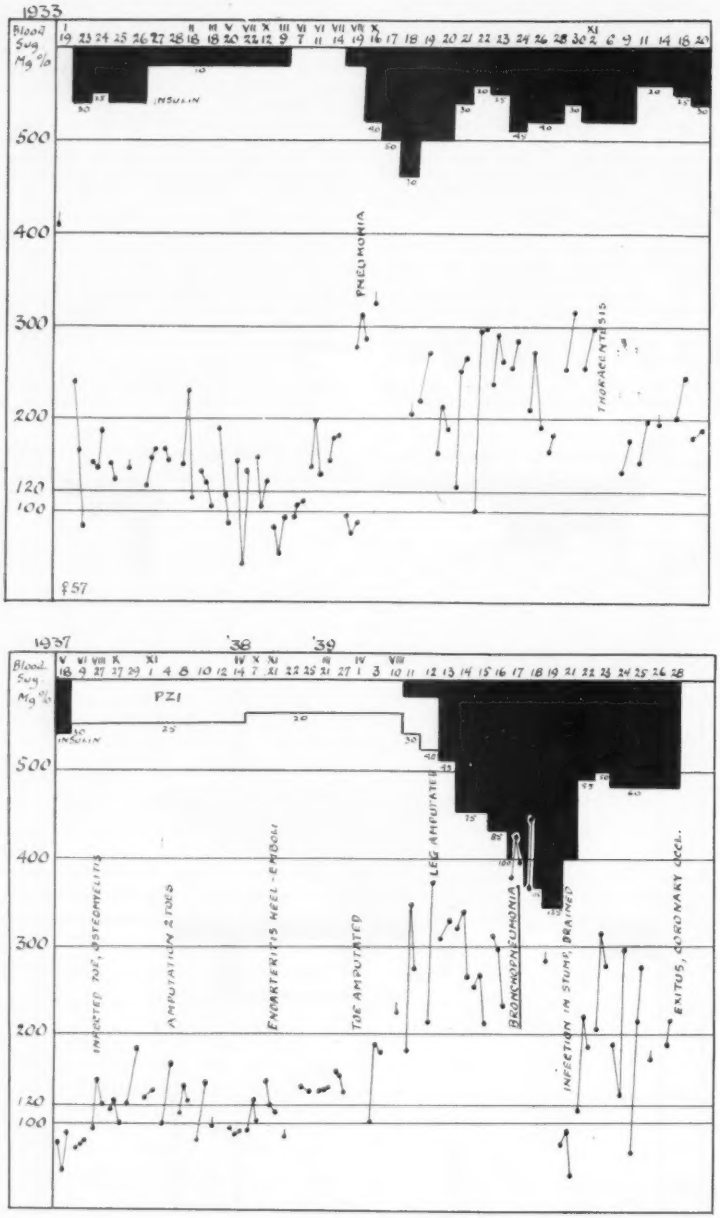

Figure 7.

but after the removal of the tonsils, the diabetic condition cleared, and diet alone provided adequate control to the time of the terminal incident.

Case 6.—A married woman, aged 34 years, consulted me because glycosuria had been discovered four months previously, when she had displayed the typical symptoms of diabetes (Fig. 6). The only significant illness prior to the development of these symptoms was cholecystitis for which cholecystectomy had been performed seven years earlier. The patient had been obese, but had lost 23 pounds since the onset

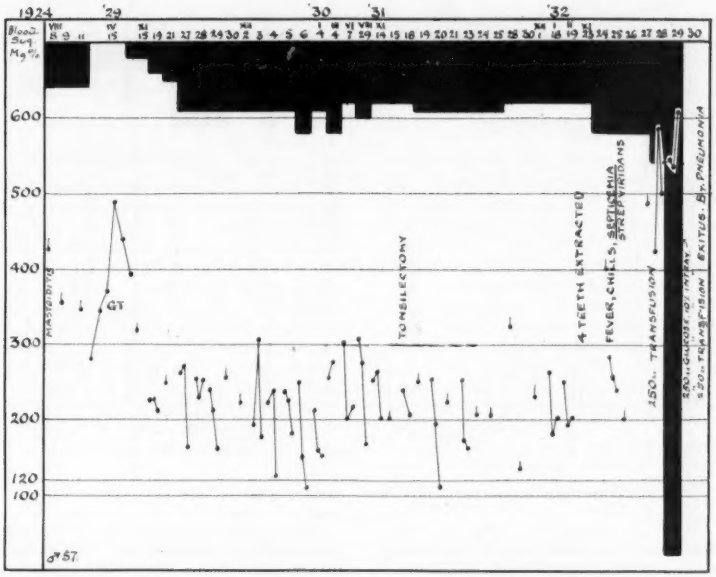

Figure 8.

of the diabetes. The blood sugar level, on entrance, was 190mg per cent five and a half hours after eating, and there was a heavy glycosuria. Insulin was administered for four months and the blood sugar came down to normal. Insulin then was discontinued for the next ten years. Nephrotomy was performed in 1936, and administration of insulin was resumed for a few days while the patient was in the hospital, but was again discontinued for another period of ten years. Then a kidney infection developed, and insulin had to be reinstated. A nephrectomy was performed and on the day the patient was to have left the hospital, she died suddenly of a pulmonary embolism.

Here, except for the upset occasioned by the kidney infection, the diabetic condition remained stationary, with only slight dietary regulation, for a period of twenty years.

Case 7.—A woman was aged 57 years when she was first seen, with a relatively mild diabetes, in 1933. She had an attack of pneumonia in 1936, which greatly increased the requirement for insulin, but afterwards, this dropped to 25 and 20 units a day, in spite of numerous untoward incidents connected with a gangrenous toe which required amputation of the leg in 1939 (Fig. 7). After this operation, bronchopneumonia again occurred along with an infection in the stump, and then a greatly increased dosage of insulin was

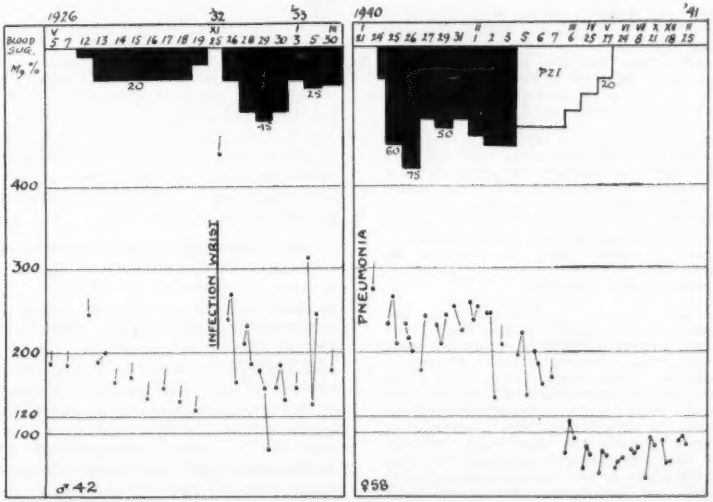

Figure 9.

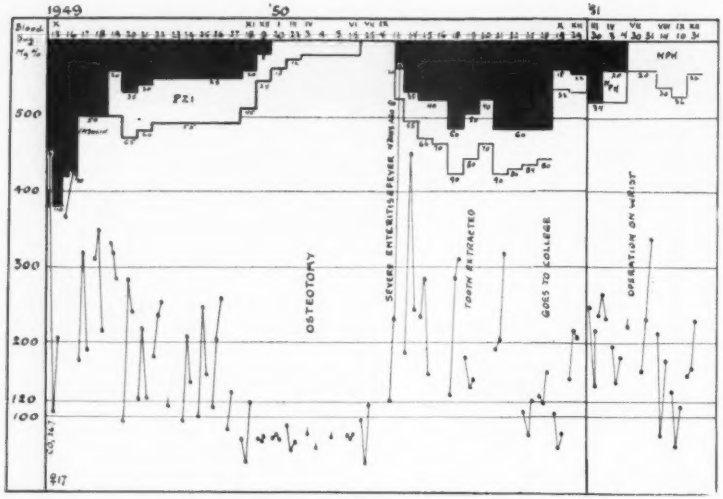

Figure 10.

required (up to 125 units a day). The patient died shortly after the onset of this infection, from coronary occlusion.

In this case, pneumonia on two occasions upset the diabetic condition considerably, although it had not been significantly aggravated by infection in the extremity.

Case 8.—When this man was first examined, at age 57 years, he had had diabetes for several years. He was travelling continually and could not control his diet satisfactorily, but in spite of this, his condition was fairly well stabilized on an average dose of 45 units of insulin. However, there was a striking change in 1932, when he had a tooth extracted elsewhere. After this, a streptococcus viridans septicemia developed and caused his death later in the same year (Fig. 8).

This patient's diabetes never had been satisfactorily controlled because of his inability to control his diet and because of inadequate observation.

Case 9.—The first case shown in Figure 9 is that of a man, aged 42 years at the time of the first examination, who had a relatively mild diabetes. It was adequately controlled with 20 units of insulin a day. Following an infection of the wrist, the insulin had to be increased to 45 units, but eventually the dosage could be reduced to 23 units. Observation on this patient extended over a six-year period.

Case 10.—The second case shown in Figure 9 is that of a woman, aged 58 years, who had pneumonia when she was first seen. The blood sugar was then 270 mg per cent and a large dosage of insulin (to 75 units) had to be given during the infection. After four months, it was possible to discontinue the insulin and the blood sugar level remained normal throughout the day. In this case, without the protection afforded by large doses of insulin during the infection, the patient most probably would have had a severe diabetes requiring insulin permanently for its control.

Case 11.—A girl, aged 17 years, was admitted to the hospital with a diagnosis of acute appendicitis, and was to have an emergency operation. Routine examination of the urine, preparatory to the operation, revealed a heavy glycosuria; then the blood sugar was determined and was found to be 450 mg per cent and the carbon dioxide was 27.6 (Fig. 10). It was evident that the patient had a severe diabetic acidosis, which often simulates the picture of an acute appendicitis. Large doses of insulin brought the blood sugar down to normal. The insulin dose was gradually decreased and after eight months, when she began to have insulin reactions on 10 units a day, all insulin was discontinued. The diabetic condition remained under perfect control for three months. Then acute enteritis developed and the temperature rose to 103 F for one day. When I saw her four days later, on September 11, 1950, there was a marked hyperglycemia. The fasting blood sugar was normal, but the level rose sharply, up to 563 mg per cent, in the evening. A heavy dosage of insulin (to 90 units a day) had to be given for thirteen days before the blood sugar receded to normal.

This case represents a typical instance of the unfavorable influence of infection on diabetes. The enteritis caused a complete upset of the carbohydrate metabolism which had become well stabilized, without insulin. The infection was certainly mild, for the temperature was elevated above normal for only one day. Had the clinical evaluation rested on a determination of the fasting blood sugar at the time I saw her after the acute infection, the whole situation would have been misinterpreted, since the fasting blood sugar was normal, even though the level later in the day was extremely high.

COMMENT

A series of eleven cases of diabetes mellitus in which an infection occurred during the time of observation has been presented. In two of these instances, there was no resulting aggravation of the diabetic state. In all the others, a considerable disturbance of carbohydrate metabolism accompanied or followed the infection, requiring a pronounced increase of insulin for periods of varying duration.

This study is presented to remind physicians of the importance of a careful check of the diabetic patient in even the slightest of infection. This is necessary in order to ascertain whether infection has caused an exacerbation of the diabetes, which is the general rule, although there are exceptions (Cases 1 and 2). This precaution is necessary even when the diabetes is extremely mild, so that the patient may be protected by an increased dosage of insulin, according to the requirements indicated in the individual case. This requirement can be judged accurately only by determination of the blood sugar three times during the day, before meals, since the fasting blood sugar alone may be completely misleading.

THE EFFECT OF OTHER LIPOTROPIC SUBSTANCES ON THE FATE OF CHOLINE AFTER ORAL AND INTRAVENOUS ADMINISTRATION

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INTRODUCTION

CHOLINE, methionine, and inositol belong to the group of substances called "lipotropic agents" because of their ability to prevent the formation of fatty liver under certain conditions of dietary deficiency, or to remove fat from the fatty livers so produced experimentally. The exact way in which fat removal is accomplished and the relation between these substances is uncertain. Recent experiments demonstrated that when choline is ingested in the human, about 60 per cent is degraded by intestinal bacteria to trimethylamine (TMA*), which is excreted in the urine and no free choline is excreted (1). When choline is injected intravenously, about 10 per cent is excreted in the urine as free choline, but only basal amounts of TMA are excreted (2).

To investigate whether the addition of methionine or inositol alter the manner in which choline is handled after ingestion or injection, the following experiments were performed; 1) a comparison of the *in vitro* degradation by intestinal bacteria of choline alone with the degradation of choline combined with methionine, inositol, or both; 2) animal and human studies in which urinary TMA excretion following the ingestion of choline was compared to the TMA excretion after ingestion of a mixture composed primarily of choline chloride, dl-methionine and inositol; and 3) a comparison of urinary choline excretion in humans after the intravenous injection of choline alone with the excretion after injection of a mixture of choline, methionine, and inositol.

MATERIAL AND METHODS

To a basic bacterial culture medium of 1 per cent tryptose and 0.5 per cent sodium chloride, choline chloride, dl-methionine, and inositol were added to make solutions with the following final concentrations: a) 1 per cent choline, b) 1 per cent choline and 0.25 percent methionine, c) 1 per cent choline and 0.5 per cent inositol, and d) 1 per cent choline, 0.25 per cent methionine and 0.5 per cent inositol. Two different human feces were tested. A dilution of each was added to 8 ml. of each of the four media. After incubation for 24 hours, 2 ml. of each medium was alkalinized and aerated. The TMA so liberated was trapped in hydrochloric acid, precipitated with Reinecke salt, and the TMA-reineckate determined as described previously (1).

*Trimethylamine is excreted in the urine mainly as trimethylamine oxide (TMAO), only a small amount appearing as simple TMA. In previous papers (1-3) urinary excretion of TMAO and TMA has been called "total trimethylamines" (TTMA). For the sake of simplicity, urinary total trimethylamines will be referred to as TMA in this paper.

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Six rats of the Wistar strain, weighing between 150-200 grams, each were fed 15 mg. choline chloride, 7.5 mg. inositol, and 3.75 mg. dl-methionine. Two control rats each received 15 mg. choline chloride alone. Forty-eight hour urinary TMA nitrogen was determined as described previously (1).

Ten patients ingested a single dose of choline chloride, equivalent to 2 grams of choline base, and one week later a mixture of choline, methionine and inositol (*) containing an equivalent amount of choline base. The urine of the first and second 24 hours was collected under hydrochloride acid and the TMA nitrogen in both samples determined by the aeration method described previously (1).

Seven patients were given an intravenous injection of 1.15 gram choline chloride (equivalent to 1 gram choline base) and one week later an intravenous injection of 0.57 gram inositol, 0.38 gram dl-methionine, and 1.15 gram of choline chloride**. The solutions were diluted in 500 ml. of 5% dextrose in water and injected by slow drip in one hour. Urine was collected from 0-3 and from 3-24 hours after the beginning of the injection.

Five patients were given twice the dose of the same solutions (equivalent to two grams choline base) diluted in 1000 ml. of dextrose in water, intravenously in two hours. In these, urine was collected from 0-4 and from 4-24 hours after beginning the injection. Urinary excretion of choline nitrogen was determined by precipitating choline with Reinecke salt as described previously (1).

*Methischol (R) (U. S. Vitamin Corporation, New York) containing in each 15 cc. 0.38 gm. choline chloride, 0.33 gm. dl-methionine, 0.25 gm. inositol, 3 mcg. Vitamin B_{12}, and liver concentrate from 12 gm. of liver.

**The mixture for intravenous use was supplied by the U. S. Vitamin Corporation, New York, in 10 cc. ampuls, each 10 cc. containing 1.0 gm. choline chloride, 0.5 gm. inositol and 0.25 gm. methionine.

RESULTS

In each case of *in vitro* degradation of choline by the bacteria present in two human feces, the per cent of choline nitrogen recovered as TMA nitrogen was not significantly altered by the presence of methionine or inositol or both in combination with choline (Table I).

TABLE I

PER CENT CHOLINE NITROGEN RECOVERABLE AS TRIMETHYLAMINE NITROGEN AFTER INCUBATION WITH HUMAN FECAL BACTERIA

Medium	Per Cent Choline N Recovered as TMA N	
1% Tryptose + 0.5% NaCl plus	Stool A	Stool B
1% Choline Chloride	54	42
1% Choline Chloride + 0.25% dl-methionine	58	40
1% Choline Chloride + 0.5% inositol	53	46
1% Choline Chloride + 0.25% dl-methionine + 0.5% inositol	55	41

The amount of TMA nitrogen excreted in the urine of the rats fed choline alone was of the same order as that found in a large group of similar animals reported previously (3). The rats fed inositol and methionine simultaneously with choline excreted the same amount of TMA nitrogen as their control litter-mates (Table II).

TABLE II

AMOUNT OF TRIMETHYLAMINE NITROGEN EXCRETED IN 48 HOUR URINE OF RATS FED CHOLINE ALONE AND IN A LIPOTROPIC MIXTURE*

Rat No.	Given	48 Hr. Urinary TMA Nitrogen Excretion (mg.)
199	Choline chloride* -	0.570
200	Choline chloride* -	0.620
201	Lipotropic Mixture**	0.600
202	Lipotropic Mixture**	0.650
203	Lipotropic Mixture**	0.590
204	Lipotropic Mixture**	0.630
205	Lipotropic Mixture**	0.580
206	Lipotropic Mixture**	0.650

*Dose equivalent to 15 mg. choline base.

**Lipotropic Mixture (Methischol (R)) in doses equivalent to 15 mg. choline base.

In humans, the urinar TMA nitrogen excretion following the ingestion of a mixture of choline, methionine and inositol was not significantly different from that following the ingestion of choline alone. In each patient, the excretion was of the same order regardless of differences between individual persons in the absolute amount of TMA nitrogen excreted. The patients with cirrhosis excreted significantly less TMA nitrogen than normal (Fig. 1).

The urinary excretion of choline nitrogen after intravenous injection of a mixture of choline, methionine and inositol was not significantly different from the excretion after injection of choline alone, in the individual person, in doses equivalent to one or two grams of choline base. However, there was considerable difference in the amount excreted by different individuals, (Table III). No untoward effects were noted upon the intravenous injection of choline alone or in combination with methionine and inositol. Occasional flushing and a moderate fall in systolic blood pressure during both types of infusions were noted. Neither necessitated discontinuance of the injection and no sequelae were observed.

DISCUSSION

The lipotropic action of choline is thought to be due to stimulation of phospholipid synthesis and transfer in the liver (4). Methionine is thought to be lipotropic because it makes methyl groups available for the synthesis of choline (5). Inositol is lipotropic under certain conditions where choline is not, presumably through the promotion of phospholipid formation, possibly involving different fatty acids than choline (6). If these agents are presented to the body simultaneously in significant quantities, it is conceivable that they will be utilized preferentially, sequentially, or in some manner different from the way they are utilized individually.

Some experience has been gained with the excretion of choline following its oral or intravenous administration in patients and experimental animals with and without liver disease and in health (1-3). An attempt was made to demonstrate some alteration of the metabolism of these compounds if presented together to the body by the simultaneous injection intravenously of all three, and comparing the urinary excretion of choline with its excretion when given alone. In patients with and without liver disease no difference in choline excretion occurred, regardless of whether methionine

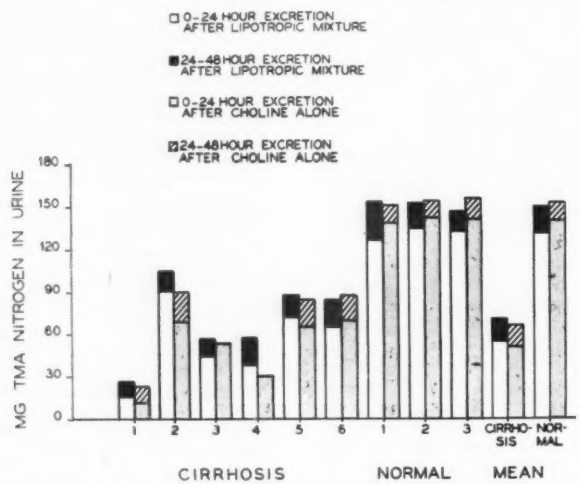

Fig. 1: Urinary excretion of trimethylamine nitrogen following ingestion of a lipotropic containing choline (Methischol (R)) and following ingestion of choline alone.

TABLE III

URINARY CHOLINE NITROGEN EXCRETION FOLLOWING INTRAVENOUS INJECTION OF CHOLINE ALONE AND IN A LIPOTROPIC MIXTURE* (mg.)

Dose	Patient	Diagnosis	Lipotropic Mixture		Choline Alone	
			0-3 Hr.	3-24 Hr.	0-3 Hr.	3-24 Hr.
1 gm. choline base	T. L.	Cirrhosis	3.30	0.57	2.90	0.49
1 gm. choline base	B. W.	Cirrhosis	5.20	2.25	4.10	2.10
1 gm. choline base	E. WA.	Cirrhosis	14.40	0.53	12.40	0.72
1 gm. choline base	J. A.	Cirrhosis	9.30	1.03	7.90	1.30
1 gm. choline base	F. H.	Cirrhosis	15.60	0.60	14.40	0.92
1 gm. choline base	W. G.	Hypertension	8.20	.....	7.0	0.44
1 gm. choline base	A. F.	Arthritis	9.70	0.70	10.80	0.60
			0-4 Hr.	4-24 Hr.	0-4 Hr.	4-24 Hr.
2 gm. choline base	A. M.	Hypertension	25.50	1.14	29.00	0.92
2 gm. choline base	E. WO.	Carcinoma	42.50	0.63	43.2	0.48
2 gm. choline base	E. WA.	Cirrhosis	26.40	0.70	26.40	0.80
2 gm. choline base	E. W.	Arterio-sclerosis	14.00	1.00	16.3	0.84
2 gm. choline base	S. A.	Hypertension	19.2	0.90	21.8	1.06

*The mixture contained in each 10cc. 1.0 gm. choline chloride, 0.5 gm. inositol and 0.25 gm. methionine.

and inositol had been given with choline or not. The safety of intravenous injection of these substances in large amounts was demonstrated. As much as 2 grams of choline chloride, 1 gram of inositol and 0.75 gram of methionine were given intravenously without ill-effect, the only untoward effects being flushing or transient drop in systolic blood pressure.

Previous studies had also indicated that choline, when given orally, to a large extent is degraded by intestinal bacteria to trimethylamine (TMA), a substance having no known lipotropic or physiologic action (7). (In fact, if TMA is ingested, it is almost entirely excreted in the urine). Therefore, much of a given dose of choline is not available for absorption from the intestine. Since several intestinal bacteria utilize choline for metabolism and growth, and others utilize methionine or inositol (8), might one find a difference in the amount of choline degradation by the intestinal contents if one feeds all three substances together? If so, this might be detectable in differences in the TMA excretion. The results of the experiments would indicate that such is not the case, that the degradation of choline to TMA in the presence of methionine and inositol proceeds in a fashion comparable to that of choline when ingested alone.

SUMMARY AND CONCLUSIONS

1. *In vitro* degradation of choline to trimethylamine (TMA) by fecal bacteria is unchanged in the presence of methionine, inositol, or both.

2. Rats fed methionine and inositol together with choline excreted the same amount of TMA in the urine as rats fed choline alone. Human experiments duplicated the experience in animals.

3. Humans excrete the same amount of choline in the urine following the intravenous injection of methionine, inositol and choline together as they do following the injection of choline alone.

4. The intravenous injection of methionine, inositol, and choline in relatively large amounts is well tolerated and appears to be without danger.

5. The presence of the lipotropic agents methionine and inositol does not appear to influence the degradation or excretion of choline after oral or intravenous administration, again pointing to the differences in the lipotropic action of these substances.

We wish to thank Dr. Hans Popper for his generous advice during the conduct of this investigation.

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EDEMATOUS BENIGN HEPATITIS*

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ALTHOUGH ACUTE hepatitis is a very common disease, its edematous form seems to be exceptional. It is met with rarely in western Europe; Bockus (2) does not mention acute hepatitis as one of the 39 causes he enumerates for ascites. Eppinger (11) ascribes great importance to the Sodium and water retention to support his well-known theory of the "serous inflammation;" he concludes that the water must be stored in the liver and spleen, because of the fact that neither edema nor ascites are evident.

We know however, that "in the icteric phase of acute hepatitis, there is an increase in the interstitial fluid compartment of the body, and a tendency to store water" (S. Sherlock, (17)). It is strange to think that fluid retention, so often met with in cirrhosis, should be so exceptional in benign hepatitis, and this is why we report here an observation of edematous hepatitis:

CASE REPORT

M.— F.—, female, 22 years old, married 5 months, had never had any child and was not pregnant. She had no history of gall-bladder or liver disease, nor anything relevant to the disease. The patient had shown no intolerance to any particular food and did not drink alcohol in any form. Her ony complaint was an occasional sore throat.

In the middle of August 1951, while camping in the Channel Islands (Jersey), she experienced slight digestive disturbances for approximately 10 days. A *jaundice* then appeared, on the 20th of August, the temperature rising to a maximum of 38° C (100,4° F). She was treated at home in the prescribed manner—various vitamins, Litrison (a mixture of lipotropic substances), Bilamid (a disinfectant of the biliary tract) and ox-bile extract. Three weeks later, the patient noticed that her face and ankles were swollen, and that she urinated very little and too often. Her physician recommended that she be hospitalized.

Upon admission, on the 16th of September 1951, the patient showed no fever; her general nutritional condition was satisfactory, in spite of the fact that her appetite had been rather poor. She exhibited no pruritus. Several enlarged cervical and axillary glands were found. The jaundice was quite pronounced, the bilirubin level in the blood (direct Van den Bergh reaction) amounted to 235 mg./l. The stools were not completely discoloured. The diuresis did not exceed 500 ml. per 24 hours; the urine contained biliary salts and biliary pigments.

There was a noticeable malleolar edema and a swelling of the face, especially marked in the suborbital areas. The abdomen was very much inflated, but the clinical examination did not reveal any evidence of ascites. The liver was small, its inferior border not palpable, its vertical measurement was determined to be 8 cm. by percussion; the sub-hepatic region was sensitive to palpation, the spleen was not enlarged.

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The cardio-vascular, pulmonary, urogenital and neurologic findings were normal. Two duodenal drainages were made (18th and 24th of Sept.), the results indicating a good gall-bladder reaction to the Meltzer-Lyon test, with concentrated B-bile. Other laboratory tests were performed and these will be discussed below (see charts).

The most probable diagnosis was *infectious hepatitis;* it should be added that the patient had had no injections in the previous months, thus excluding homologous serum hepatitis. Therefore, in addition to the treatment begun at home, we prescribed dehydrocholic acid, intravenous plasma and glucose, liver extract, and an hydrolysate of amino-acids (Nesmida) orally. The patient, because of her lack of appetite, certainly did not eat more than 50 gm. of protids and 1600 calories.

Three days after she entered the hospital, the clinical signs of *ascites* appeared very rapidly and, as a result, it was necessary to perform three abdominal punctures (2,0. 3,5 and 1,6 l., on the 25th of Sept., 1st and 15th of Oct.). The liquid obtained had the classical characteristics of a transudate, the culture of which was sterile. Therefore the possible diagnosis of peritoneal tuberculosis was eliminated.

A renal etiology could also be dispensed with, on the basis of following facts: upon entrance, the urine contained only traces of albumin and several granular, casts, and these disappeared in a few days; the blood pressure remained at a normal, low level; the urea content of the blood never exceeded 0,25 gm./l.; the renal functions were satisfactory, according to the laboratory tests; the agglutination for leptospirosis Weil was negative.

In view of this recurrent ascites, a cirrhosis or a subacute necrosis of the liver was feared: the liver remained small and the protein level in the blood was very low (52 and 43 g./l.). On the other hand, the investigation for leucine and tyrosine in the urine proved negative; a paper chromatogramme* showed a very small quantity of amino-acids excreted in the urine; some flocculation tests were negative (Thymol turbidity, Takata), some others positive (Céphaline-cholesterol); the blood prothrombin level was at 65 or 80%; the galactose tolerance test gave normal values; the non-protein nitrogen had not increased. All these facts, as well as the clinical picture pointed to a benign condition.

In spite of all the therapeutical methods employed, including a sodium-free diet, the diuresis was not ameliorated, and the volume of the ascites grew. Suddenly, and apparently without relation to treatment, the diuresis began to increase during the sixth week of her hospitalization (25th of Oct.); the patient lost weight rapidly (3,100 Kg. in 6 days) and recovered her appetite; the ascites and swelling of the face diminished and disappeared.

After losing this excess tissular fluid, the patient

*By the courtesy of Prof. E. Martin's laboratory.

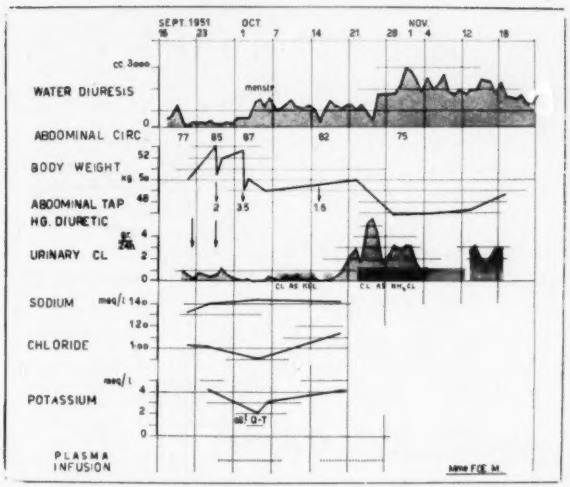

CHART I

gained weight progressively, without recurrence of edema. Her general condition improved considerably. The jaundice diminished slowly and the patient still showed a bilirubinemia of 19 mgm./l. a few days before leaving the clinic. On the 18th of Nov., after being hospitalized for more than two months, the patient left for convalescence in the mountains.

Four months later, she returned for a control examination: it was found that the liver was still small; the "icterus index" was normal (5); the protein blood level was at 78 gm./l.; all the flocculation tests were negative; only the Volhard water test showed a diuresis slightly insufficient in the first four hours. She explained that before menstruating, diuresis diminishes, her face becomes swollen, her waist line increases, and that everything returns to normal when menstruation occurs.

The FIRST CHART shows the variation in daily urinary volume, body weight, daily urinary chloride, and level of electrolytes in the serum.

One can see that the *water diuresis* which was very small at the beginning, improved slightly when menstruation occurred and increased very definitely in the sixth week. This coincided with the giving of ammonium chloride.

The *body weight* curve shows the rapid gain at the time ascites was accumulating. Despite the fact the patient was put on a salt-free diet and was given xanthic and mercurial diuretics, the tendency to reform ascites persisted. The sudden loss of weight corresponded to the abundant water and Cl diuresis; and thereafter bodyweight slowly picked up, as the patient regained her appetite.

During the time ascites and edema were present, daily *urinary chloride* was very small, less than that ingested. This was especially apparent during the period in which the patient received a weighed amount of KCl: the amount of chloride excreted was less than that given in the form of KCl. Mercurial diuretics only enhanced very slightly Cl excretion. This began to increase before NH_4Cl was given, and a few days later Cl output definitely exceeded Cl intake. Sodium probably behaved similarly to chloride, and this negative balance of extra-cellular electrolytes caused the weight loss and the disappearance of ascites and edema. The pattern of electrolytes was characteristic of hypokalemic hypochloremic alcalosis during the phase of ascites. The chloride level came back to normal before the diuresis increased; it is possible that it was under the influence of the KCl.

The SECOND CHART shows the variations of the level of bilirubin and proteins in the plasma. The lower line traces daily urinary urea excretion. The rate of decrease of the bilirubinemia remained constant, despite the formation and the disappearance of edema and ascites.

The level of *plasma proteins* was quite low during the period of fluid retention; both the albumins and the globulins were decreased. The level of proteins had returned to normal when the strong diuresis occurred.

The *urea-excretion curve* is quite puzzling. During the first 4 weeks, urea excretion varied around 3 to 4 gm./24 h. Simultaneous determination of total urinary nitrogen showed that roughly 80% of the nitrogen was eliminated as urea nitrogen. A urinary paper chromatogramme showed a very low excretion of amino-acids. Therefore, the daily urinary nitrogen was around 2 gm. a day, which is within the range of the lowest values recorded in the literature (1). There was no diarrhea nor vomiting. The patient was in a state of poor caloric intake, that is to say she was not in a condition favorable to a minimal protein catabolism. In her state of caloric intake, one would expect a daily urea excretion of 10 to 15 gm./24 h. When the strong diuresis occurred, urea excretion came back to normal values.

DISCUSSION

Portal hypertension favours ascites; this is the reason why it is so often observed in cirrhosis. Acute hepa-

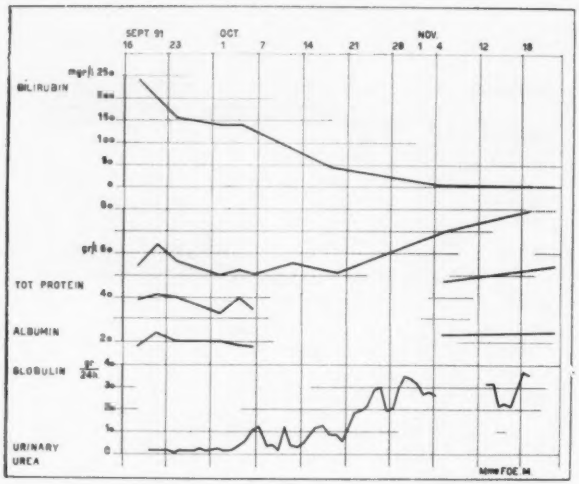

CHART II

titis, on the contrary, evolves without any trouble in the portal district, and *edema must be mainly related to liver-cell dysfunction*. As a consequence, dropsy is met with frequently in the severe form of hepatitis, i.e. liver necrosis; Lepehne, Umber described it in Germany in 1921 and 1922. Among the most recent publications on this subject, Lucké (14) had an opportunity to study 175 American soldiers during World War II, and came across ascites in 2/3 of them; but abdominal fluid appeared only during the last days of of the illness, before death. Salvesen and Loedoen (16) found ascites in 11 patients in 26 cases of malignant hepatitis under observation in Norway and this fluid accumulation never occurred in those who recovered later.

The *hydropic form of acute benign hepatitis* was described, by Le Damany (13) in 1914, amongst alcoholics who did not yet suffer from cirrhosis. Cachera, since the first two observations published with Caroli and Deparis (9), particularly pointed out the "forme hydropique de l'ictère catarrhal." The clinical picture of this "benign edematous hepatitis" is as follows, corresponding, except a few details, with the one found in our patient:

a) This hepatitis has most probably an infectious (virus) origin, but it cannot be considered as "epidemic," because it appears *sporadically*;

b) The ascites is accompanied by *no sign of portal hypertension*: neither spleen enlargement nor collateral circulation;

c) The edema *does not run parallel with the jaundice*; the water retention often develops when the icterus is retreating;

d) The diuresis is usually not diminished and, in any case, the *renal functions are normal*;

e) The *evolution* of this particular illness is *very long*: 14 weeks, in our case, between the beginning of the jaundice and the moment the patient left the hospital (not completely discoloured).

Cachera (5) does not think that the *prognosis* of cases with fluid retention is worse than in other forms of hepatitis. On the other hand, Monges (15) points out that it is often a sign of precocious sclerosis, which could be transformed later in cirrhosis; therefore he considers the prognosis of the "ictero-edematous syndrome" being rather poor.

PATHOGENESIS

The pathogenesis of ascites in case of hepatic cirrhosis has been extensively studied (10). But the pathogenesis of fluid retention during hepatitis is less known, and has been investigated by Cachera and Darnis (7), and Labby and Hoagland (12). These authors have shown that during any cases of hepatitis, when no fluid retention can be detected clinically, an *increase of the extracellular fluid volume* can be recorded. They measured Sulfocyanate and Thiocyanate space. Changes in membrane permeability which Cachera and Darnis (6) have detected during hepatitis, throw doubt on the value of Sulfocyanate and Thiocyanate as means of measuring extracellular fluid volume changes. The fact that, in rare cases, actual edema and ascites occur during hepatitis gives strong support to their measurements.

Using the Landis method, Cachera and Darnis (6) have also studied *capillary permeability* during the course of benign hepatitis. They have observed that capillary permeability is increased at the same time as the increase of extracellular volume can be measured, and they feel that a causal relationship may exist.

The complexity of factors involved in fluid retention of hepatic origin has been stressed (8). Our case shows that several metabolisms were disturbed.

The *water metabolism* was modified: ingested water was not readily excreted. Brulé and Cottet (3) have described this anomaly during jaundice, as well as the

inversion of the nycterine rhythm of water excretion. Ralli and her group (18) have demonstrated in cases of ascites with cirrhosis of the liver that the abnormal tendency to retain water may be due to the presence of an antidiuretic substance, probably similar to antidiuretic hormone. We made no measure of capillary permeability.

The *electrolyte metabolism* was also modified, in that the extracellular electrolytes were abnormally retained. The unfavourable effect on ascites of an increased intake of NaCl has been known for a long time, and a very low salt intake is one of the best measures to diminish the recurrence of ascites. We have observed during the phase of ascites a hypokalemic hypochloremic alcalosis. Having unhappily made no study of the adrenal function, we can not say if a hyperfunction occurred at that time (or a decreased destruction of the adrenal hormone).

The *protein metabolism* was disturbed. The protein level was very low, but we did not observe a change in the Albumin/Globulin ratio, which was thought to cause edema because of the lowering of the oncotic pressure of the plasma. Lowering of plasma protein or inversion of the A/G ratio is not always observed in cases of ascites in cirrhosis (8).

SUMMARY

A case of infectious hepatitis with complication of transient edema and ascites is reported. The fluid retention was neither of cardiac nor of renal origin and was most probably related to the liver disease.

Very few similar observations are found in the literature and demonstrate clinically the tendency to retain extra-cellular fluid, which can be shown by laboratory measurements in any case of hepatitis.

The pathogenesis of fluid retention of hepatic origin is briefly reviewed.

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EARLY EFFECTS OF ACTH ON ARTERIAL AND VENOUS BLOOD GLUCOSE AND ON RENAL GLUCOSE EXCRETION

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With the technical assistance of Julia F. Allen

THE ADMINISTRATION of ACTH to human subjects has been reported to produce an early renal glycosuria (1, 2, 3, 4, 5, 6, 7) which was ascribed to the inhibiting effect of the hormone on tubular reabsorption of glucose. Since most of the reported studies have dealt exclusively with venous blood sugar values, we have found it difficult to accept their conclusions. The arterial and venous blood glucose levels do not maintain a constant relationship (8) and it is the arterial blood, not venous, which is filtered at the glomerulus.

We therefore proposed to investigate the early changes in carbohydrate metabolism induced in man by ACTH, by employing a single dose of the hormone with and without glucose loading, measuring the arterial and venous glucose levels simultaneously.

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Submitted May 8, 1952.

MATERIAL AND METHODS

Oral glucose tolerance tests, using 100 gm. of glucose in 250 cc. of water flavored with citric acid, were performed on six ambulatory subjects maintained on a diet adequate in calories and protein, and providing an intake of 150-200 gm. of carbohydrate daily. After an interval of at least two weeks the tests were repeated following intramuscular administration of 50 mg. of ACTH Armour Standard just prior to the ingestion of glucose.

Subjects 1 and 3 had a history of moderate spontaneous hypoglycemia. Subject 2 had had six grand mal seizures in six months, and subject 4 renal glyco-

TABLE I

EFFECT OF ACTH ON BLOOD GLUCOSE AFTER GLUCOSE LOADING (CASE 1-6) AND DURING FASTING (CASE 7). a: WITHOUT ACTH; b: WITH ACTH. ALL VALUES EXPRESSED AS MG. PER 100 CC. OF BLOOD.

Time	Fasting				½ hr.				1 hr.				2 hrs.				3 hrs.				4 hrs.				5 hrs.			
Blood	Arterial		Venous		Arterial		Venous		Arterial		Venous		Arterial		Venous		Arterial		Venous		Arterial		Venous		Arterial		Venous	
	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b	a	b
Case 1	73	73	71	74		117		93	100	87	83	74	105	117	93	89	102	100	102	90	65	71	70	74	80	67	72	72
Case 2	68	77	70	81		83		83	105	121	95	102	125	105	98	90	93	105	105	83	87	93	87	83	83	67	83	61
Case 3	72	58	64	71		101		101	114	125	83	125	91	114	80	77	108	105	73	93	89	91	71	80	49	74	61	69
Case 4	79	93	84	83					172	142	133	133	166	138	125	117	132	111	90	80	124	108	90	83	69	65	59	59
Case 5	90	105	83	91	222	170	170	125	200	170	150	114	89	110	85	100	43	102	45	85	80	78	70	90	80	90	74	83
Case 6	74	71	74	78	242	240	180	190	286	290	258	224	77	95	86	81	51	57	52	49	56	64	60	69	67	72	66	75
Case 7	80	87	80	83	100	105	83	93	86	91	80	83	55	83	83	87	93	87	80	83	76	80	83	83	71	83	80	83

suria of over twelve years' duration. Subject 5 had been under psychiatric care for four years for psychoneurosis. Though he had no complaints referable to the gastro-intestinal tract, his glucose tolerance curve indicated accelerated absorption of sugar from the gut; an X-ray examination was then secured and revealed a duodenal ulcer with rapid emptying of the stomach. The sixth subject had a gastrectomy and gastroenterostomy done two years prior to this study.

The effect of ACTH on the blood glucose content in the fasting state was studied in one subject (Case 7). He had had a duodenal ulcer, confirmed by X-ray, but was free from ulcer symptoms and had consumed a normal diet for several weeks prior to both tests.

All tests were carried out after a preliminary fast of fourteen hours. The venous blood was drawn at the bend of the elbow without the use of a tourniquet. Since the glucose content in the capillary blood has been shown to parallel that in the arterial blood, (9, 10, 11, 12), blood from fingertips was obtained simultaneously with venous blood samples. The Folin-Wu method following protein precipitation according to Somogyi (13) was used in the venous blood, and the Lauber-Mattice method (14) in the capillary blood. The good agreement between the two methods has been reported elsewhere (8). The urine specimens were collected a) at fasting, b) at frequent intervals during the test period and c) after completion of the test until the next morning to cover the remainder of the 24 hour period. All specimens were tested for glucose with Clinitest tablets, and those found to give positive reaction were quantitated with Benedict's reagent (15).

RESULTS

Figures 1 and 2 and Table I show that one 50 mg. dose of ACTH had no consistent effect on the elevation of arterial and venous glucose following oral administration of glucose. Both fast tests showed an initial small rise in the arterial curves following which there were no significant fluctuations in the blood glucose content in the ACTH test.

Renal glycosuria was recorded in two tests in which ACTH was given concomitantly with glucose by mouth. Subject 4 had had renal glycosuria for over twelve years. In the control test she had a small amount of sugar in the urine (0.075 gm.) in the fasting state with an arterial blood glucose of 79 mg. per cent, and after glucose continued to excrete sugar even though the arterial blood glucose peak did not exceed 172 mg. per cent. In the ACTH test she showed 0.15 gm. of sugar in the urine with a fasting arterial blood glucose

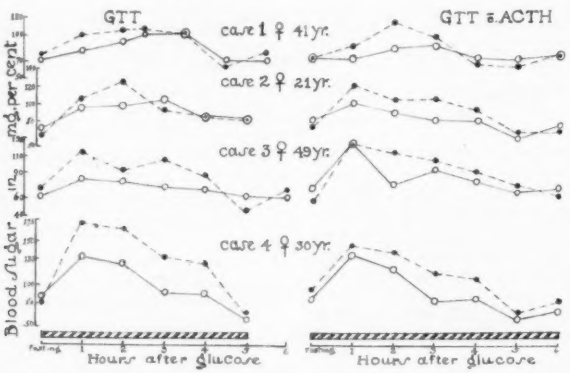

Fig. 1: Four cases with normal or low control glucose tolerance curves. On the left side are represented the control glucose tolerance tests (GTT) and on the right side glucose tolerance tests following intramuscular administration of 50 mg. ACTH (GTT with ACTH). The solid line curves with circles designate the venous and the broken line curves with dots the capillary true blood glucose concentrations. The bars with slants in Case 4 indicate the time during which glycosuria was recorded.

of 93 mg. per cent, and this glycosuria continued throughout the test period even though the arterial blood glucose did not rise beyond 142 mg. per cent. The total amount of sugar excreted in five hours of the control test was 3.84 gm. and after ACTH 4.35 gm.

The other patient (Case 5) exhibited in the control test a fleeting glycosuria of 0.3 gm. when his arterial blood glucose rose to 222 mg. per cent. In the ACTH test glycosuria appeared within fifteen minutes from commencement of the test and continued until the third hour specimen was collected. The total amount of excreted sugar was 0.23 gm. and the urine remained sugar free during the remainder of the 24 hour period. The arterial blood glucose was only 133 mg. per cent at twenty minutes after ingestion of glucose and did not exceed 170 mg. per cent during the balance of the test period. In another glucose tolerance test without ACTH, performed a month later, the arterial blood glucose reached the peak value of 167 mg. per cent within the first half hour; but the urine remained sugar free throughout the test period as well as during the remainder of the 24 hour period.

DISCUSSION

The technical difficulties involved in taking 14 to 16 blood samples from each subject in the course of each test period have forced us to confine this investigation to but 7 subjects. However, this admittedly small number of experimental subjects compares favorably with that in other reported studies of early changes in the carbohydrate metabolism produced by ACTH. Also, the inclusion of a case of long-standing renal glycosuria and of two cases with rapid intestinal absorption of sugar permits a better evaluation of observations herein recorded.

In the present study, a single 50 mg. dose of ACTH given intramuscularly failed to produce a consistent or significant increase in arterial blood glucose peaks above those in control tests. This was particularly apparent in the patient with rapid glucose absorption from the gut as a result of gastroenterostomy (Case 6), as well as in the fast test. That a single dose of 50 to 100 mg. of ACTH given intravenously fails to produce significant changes in the blood sugar of fasting individuals was reported by Sayers et al. (16). In agreement with our observations is also the work of Constantinides et al. (17) who found that in fasted rats, ACTH had no effect on the blood sugar content.

Some of our subjects (Cases 1, 3, 6) did show an increase in the peak arterial glucose values when given ACTH and glucose. The differences, however, were small and not outside the possible range of variation which may be observed in repeated glucose tolerance tests unmodified by the addition of ACTH.

Since glucose which reaches the renal tubules is derived from arterial blood by way of the glomerular filtrate, studies of renal glycosuria must be based on determinations of the arterial blood glucose if they are to reflect the physiological facts. Cases 5 and 6 who manifested rapid glucose absorption from the intestinal tract, were selected for this investigation because such subjects approximate more closely than do normal individuals the renal threshold for glucose, which is estimated to be about 200 mg. per cent in the arterial blood (18, 19). As such they should afford a more sensitive index of minor depressions of the renal threshold.

Case 5 exhibited a convincing drop in his renal threshold as a result of ACTH administration. In Case 6 the normal renal threshold was exceeded in both glucose tolerance tests. However, despite very similar curves, the loss of sugar in the urine was only

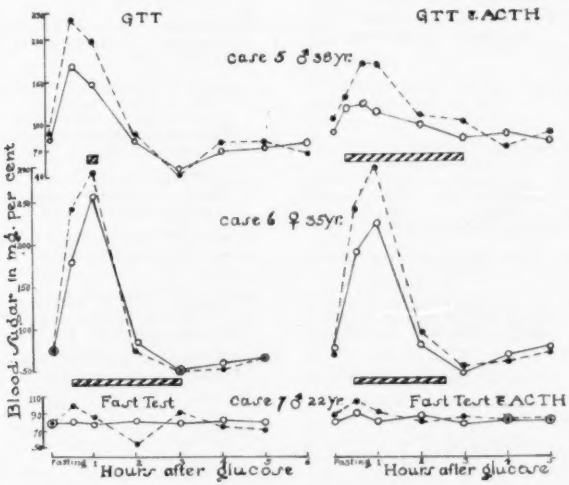

Fig. 2: Cases 5 and 6 represent two subjects who in control tests exhibited marked hyperglycemia due to rapid intestinal absorption of glucose. In Case 7 blood glucose variations in the fasting state (on left) are compared with those recorded during the fast test after administration of 50 mg. ACTH (on the right).

0.4 gm. in the control test as against 2.15 gm. in the ACTH test, suggesting that ACTH may have lowered this patient's renal threshold for glucose also.

The subject with established renal glycosuria (Case 4) excreted 0.51 gm. more of sugar in the ACTH than in the control test. This small difference may not be significant, for in a subject with renal glycosuria the amount of sugar excreted may vary from one day to another. In a recent note to the Editors of Lancet, de Filippis and Iannaccone (20) mentioned a case of established renal glycosuria in which administration of 36 and 24 mg. of ACTH daily increased the tubular reabsorption of glucose and raised the renal threshold for glucose. Whether venous or arterial blood was used in the determination of the renal threshold was not stated.

No glycosuria was noted in the remaining ACTH tests of this series. Pertinent in this connection are the studies of Alexander et al. (21) who found little change in the tubular mass for glucose (TmG) in seven subjects given ACTH.

SUMMARY

1. To evaluate early effects of ACTH on the carbohydrate metabolism in man, a study was made of variations in arterial and venous blood glucose content and the urinary glucose excretion in seven subjects given a single 50 mg. dose of ACTH, both with and without oral glucose loading.

2. At the employed dosage level, the hormone failed to produce a consistent or significant increase in arterial blood glucose peaks in excess of those in control tests.

3. A lowering of the renal threshold for glucose as a result of ACTH administration was recorded in only one subject who in the control test exhibited glycosuria well correlated with arterial hyperglycemia. In a case of long-standing renal glycosuria a single dose of the hormone failed to augment significantly the urinary glucose excretion.

4. Our data do not corroborate previous reports on the constancy of renal glycosuria as an early effect of ACTH.

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INHIBITION OF LIVER XANTHINE OXIDASE ACTIVITY IN RATS

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IT HAS BEEN reported (1) that certain substituted chalcones function as effective inhibitors of xanthine oxidase in vitro. Other substances which are effective in vitro inhibitors of the enzyme have been reported to be inactive, or of mixed activity, in the body. Gray and Felsher (2) showed that p-aminophenol was active in vitro, but inactive in vivo. Pteroylglutamic acid has been reported (3, 4) to be effective as an inhibitor of liver xanthine oxidase in vivo in chicks, but ineffective (5) in rats. In view of possible therapeutic applications of the principle of xanthine oxidase inhibition, the above findings made it of interest to determine the in vivo effects of the chalcones which had been reported (1) to be active in vitro.

Experimental

Testing was limited to one compound, 3, 3', 4, 4'-tetrahydroxy chalcone. This had been found to have an inhibitory effect on xanthine oxidase in vitro at a concentration of 0.0001 mg. per cc. Rats were fed on a basal diet of ground Purina Chow, with the chalcone being incorporated into the diet to the extent of 0.5% by weight in the experimental group. At the end of 2 weeks on the diet the rats were sacrificed and the liver xanthine oxidase activity determined manometrically by a modification of the method of Axelrod and Elvehjem (6), as previously reported (1).

Liver was ground with sand in 3 volumes of 0.039M phosphate buffer of pH 7.4, containing equal amounts of sodium and potassium ions. The homogenate was then centrifuged and the supernatant used in the experiment. The Warburg apparatus was used for determination of the activity of the tissue extract. In the center cup was placed 1.7cc. of the extract. The center well contained 0.4cc. of 10% KOH and a small piece of rolled up filter paper, while the side bulb contained 0.15cc. of 0.05M xanthine in 0.05M NaOH.

The cups were attached to the manometers and allowed to come to temperature equilibrium (37°) for 10 minutes. The stopcocks were then closed and readings were taken every 10 minutes for 40 minutes in order to determine the rate of endogenous oxygen uptake of the tissue extract. At the end of the 40 minute period this figure had usually fallen to a low, constant value. The contents of the side bulb were then tipped into the center compartment and readings were taken at 15 minute intervals for 45 minutes. Controls were run without added xanthine to give figures for endogenous oxygen uptake. These figures were subtracted from those obtained with the cups containing xanthine and the difference was taken as being due to the oxidation of xanthine alone. Xanthine oxidase activity was expressed in units (c. mm. of O_2 uptake per gm., dry weight, of liver per hour), as suggested by Westerfeld and Richert (5).

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Submitted April 1, 1952.

Results and Discussion

The results showed a definite inhibitory effect of the chalcone on liver xanthine oxidase activity. The average activity in the control rats was 1,200 units. An identical figure had been obtained previously on several hundred rat livers assayed in another investigation (1). A group of 10 rats which had been fed 3, 3', 4, 4'-tetrahydroxy chalcone gave an average liver xanthine oxidase activity of 600 units, representing a drop in activity of 50% from the controls.

There can be little doubt of the statistical significance of these results, although there is naturally a considerable variation in the individual figures. The highest value found in a rat which had been fed the chalcone was 840 units; only 12% of the control animals gave values lower than this. Five of the experimental animals, or 50%, gave values of 500 units or lower; figures this low occur in less than 5% of the controls. All the experimental figures, therefore, fall within the extreme low range of the control probability curve.

The effect on xanthine metabolism of this inhibition of xanthine oxidase activity is not known. There was found to be no significant difference in blood uric acid levels between animals being fed the chalcone and controls. However, all the animals of course had initially normal uric acid levels; it is possible that an effect would be obtained in pathological conditions characterized by high blood uric acid levels. Work along these lines is in progress.

Summary

3, 3', 4, 4'-Tetrahydroxy chalcone, an effective inhibitor of liver xanthine oxidase in vitro, has been shown to produce an inhibitory effect in vivo in rats.

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ABSTRACTS ON NUTRITION

CONRAD, S. W.: *The psychological causes and treatment of overeating and obesity.* Amer. Pract. & Dig. Treat., 3, 6, June 1952, 438-444.

While Conrad reviews the various elements involved in obesity, and advances no original hypotheses, his paper is chiefly valuable for showing that many people overeat "to relieve tension." He thinks that if tension can be removed by psychotherapy, overeating will gradually cease and weight return to normal although, of course, the patient should be placed on a diet. A team consisting of an internist, dietitian and psychiatrist at a Nutrition Clinic is briefly described.

MOORE, N. S., SCOTT, M. L., WALLACE, C. S. AND FIALA, G.: *Orally administered citrovorum factor in the treatment of pernicious anemia with neurological manifestations.* New York State J. Med., Nov. 1951, 2645.

Citrovorum Factor (C. F.), manufactured by Lederle, at present only for experimental purposes, was completely successful in the treatment of a case of pernicious anemia, both hematologically and neurologically. 10 mg. daily seemed to be the correct dosage for this patient. "C. F." is chemically related to folic acid, and may serve as a new approach to the study of pernicious anemia.

LEE, R. E., TANAKA, S. AND HOLZE, E.: *Nutritional factors in hemodynamics. II. Hypertension during pteroylglutamic acid administration to Albino rats.* Circulation, V. 6, June 1952, 903-906.

The authors determined blood pressure levels and vitamin C concentrations in rats treated with folic acid. After 6 weeks' treatment there was a significant elevation of blood pressure. The injections of folic acid were associated with numerous wedge-shaped fibroblastic lesions of the renal cortex. Under induced conditions, folic acid may exert a possible *antilipotropic* influence, and it is well known that in rats a choline deficiency in early life produces hypertension.

MUKHERJEE, C.: *Studies on carbohydrate metabolism in toxemia of pregnancy.* J. Indian Med. Assn., XXI, 7, April 1952.

The present paper deals with sugar mobilization in toxemia of pregnancy. Mobilization of sugar was impaired in eclampsia and in severe pre-eclampsia. When toxemia was of a mild degree, the results resembled those in normal pregnancy. However, in normal pregnancy the mobilization of sugar in the body was less than that in normal non-pregnant persons. The diminished sugar metabolism does not seem to be due to a deficient consumption of carbohydrates. It is probably related to the state of vascular spasm and the functional status of the pituitary gland.

YUDKIN, J.: *Effect of liver supplement on growth of children.* Brit. Med. J., June 28, 1952, 1385-1389.

Experiments with rats showed that growth was significantly improved when a powdered preparation of liver was added to a supposedly complete stock diet. A similar preparation was given to normal children of 2 years of age at the rate of 1.2 gms. per day. After 13 weeks the 32 children gained ¼ inch more in height and 10 ounces more in weight than the 28 control children. The author does *not* believe that the dietary factor responsible for this improved growth was vitamin B_{12}.

BROWN, H. B. AND PAGE, I. H.: *Mechanism of iodide action on cholesterol metabolism.* Circulation. V. 5, May 1952, 647-656.

Iodide retards or prevents hypercholesterolemia and the development of experimental atherosclerosis in rabbits. Protection is estimated from reduction of plasma and/or hepatic cholesterol. Small doses of iodide do not protect. Iodide in large doses prevents hypercholesterolemia resulting from exogenous cholesterol and reduces hepatic cholesterol. This effect is independent of the thyroid gland and is not related to "thyroxine-like" plasma iodine. The influence of iodide on cholesterol metabolism seems to be related to the presence of a butanol-soluble protein-bound iodine compound in the plasma.

CONWAY, H.: *Megaloblastic anaemia in young adults: etiological importance of idiopathic steatorrhea.* Brit. Med. J., May 24, 1952, 1098-1102.

Seven cases diagnosed as Addisonian pernicious anemia before the age of 30, in the period 1937-49, were reinvestigated during 1950. Alimentary symptoms were insignificant, but in 3 patients the initial response to parenteral liver was sub-optimal. The diagnosis of pernicious anemia was confirmed in 3 patients; but four, including the three who responded poorly to liver in the beginning, were proved to be suffering from idiopathic steatorrhea. The steatorrhea was not gross or apparent, but occult, and fat balances were required to detect it, and the detection of defective fat absorption was conclusive. No evidence of loss of the fat soluble vitamins D and K was found. The therapeutic importance of accurate diagnosis is obvious since these cases improved, as a rule, on free folic acid therapy. Histamine-fast achlorhydria is not very common in idiopathic steatorrhea and an adequate response to parenteral liver is seldom obtained. Therefore, in cases of apparent pernicious anemia which respond poorly to liver or vitamin B_{12}, the possibility of occult steatorrhea should be kept in mind.

RICKARDS, A. G.: *Megaloblastic anemia of infancy.* Brit. Med. J., June 7, 1952, 1221-1227.

Rickards describes a case of megaloblastic anemia in an infant which quickly responded to 10 mg. folic acid. Later, following a relapse, a daily dose of 10 mg. folic acid was given and proved effective. The disease appears to be due to folic acid deficiency, possibly on the part of the mother. Many cases now have been reported. While the blood smear and marrow picture closely resemble those in pernicious anemia, the latter diagnosis ought not to be made unless there is histamine-fast achlorhydria and unless the case responds to, and is maintained by liver extract, a preparation which frequently is without effect in the megaloblastic anemia of infancy.

AMER. JOUR. DIG. DIS.

EDITORIAL

OVEREATING

The general thesis that people overeat to relieve tension has been advanced by many psychiatrists as a fundamental conception in the management of obesity. It is undoubtedly true in many cases, but there are other cases of overeating where no "tension" exists. In other words, there is such a thing as inordinate appetite as a primary condition. Furthermore, there is such a thing as pure gluttony, yet many gluttons do not get fat. The ones that I have known were of slender proportions. There was one case of a priest's private servant, a man of thirty, who regularly ate enormous amounts of foods. Occasionally some of the neighbors invited him to dinner in order to furnish a spectacle. I saw him eat at one meal two whole chickens, two loaves of bread, twelve boiled potatoes, one whole pumpkin pie, besides liberal helpings of vegetables, pickles, relishes and approximately a quart of black tea. This man was obviously a high-grade moron. The main point is that he never weighed more than 135 pounds. His psychological make-up was incapable of "tension," and his body shouted defiance to the idea that overeating necessarily produces obesity. A second case was a Chinese whom I found lying on his face on the floor with acute peritonitis. Operation revealed that his stomach had ruptured soon after eating twelve beefsteaks at one sitting. He was a man of slight build and his associates stated that he had always been given to overeating in the restaurant where he worked.

There are lots of thin men who habitually overeat, but never get fat. Consequently, it is time to revise some of our thinking about obesity. While we subscribe to the thesis that a fat man is so because he has eaten too much, we submit that this is not the only cause, otherwise we would have more fat men. Nevertheless, given a fat man, we must induce him to eat less, if we would cure his obesity. We believe there are many other *physiological* factors, besides supernutrition, which produce obesity. We feel that they are of greater importance than the psychological factors. But what are they?

BOOK REVIEWS

DIAGNOSTIC ELECTROENCEPHALOGRAPHY. Hans Strauss, Mortimer Ostow, Louis Greenstein. With a foreword by Leo M. Davidoff. XIII plus 282 pages, 46 illustrations, Grune & Stratton, 1952, $7.75.

This book addresses itself to the medical student, the physician who wants to be informed about the basis, practical application and diagnostic value of electroencephalography, as well as to the specialist who wants to apply this method himself.

The first part deals with general aspects of the electroencephalogram, beginning with a history, the equipment and the recording method. It goes on to describe the components of the record, constituting normal and abnormal electroencephalograms. The physiology of the electroencephalogram, its changes accompanying psychic function and metabolic alterations are treated in special chapters. Characteristics of the normal electroencephalogram in adults and children are discussed and a classification of various types of abnormal electrœncephalograms is presented.

Part II describes the types of electrœncephalograms occurring in patients with various disorders, not only those with primary diseases of the nervous system, but also those with disorders arising outside the nervous system and with exotoxic disturbances. A special chapter is dedicated to the disturbances of the carbohydrate metabolism including hypoglycemia, relative hypoglycemia, diabetes and posthypoglycemic encephalopathy. The electroencephalogram in mental disorders, including the psychoneuroses and psychosomatic disturbances, is dealt with in detail.

The third part is dedicated to the diagnostic evaluation of the electroencephalogram. This part is of particular value to the physician who wants to know whether the electroencephalogram will be of value to him in solving a particular diagnostic problem. Tables show clearly in which conditions normal or certain types of abnormal records can be expected.

There is an extensive bibliography. 46 illustrations show the various types of records.

This book is distinguished by the clarity and simplicity of the presentation of a subject which is still relatively young and which many of us have not approached because there was no short and systematic presentation of the subject. The lack of such a presentation is an excuse no more after this book is available. We agree fully with Dr. Davidoff, who says in the foreword: "In this book, based on many years of experience, with a very large and diversified clinical material, Drs. Strauss, Ostow and Greenstein have shown us the boundaries of this field, and presented us with the tools to explore it to the limits."

Franz J. Lust.

RETOUCHES AU TABLEAU CLASSIQUE DU DIABETE. Pierre Mauriac, Masson et Cie., Paris 6, France, 1952, 520 francs.

This volume of 104 pages indicates how our conceptions of diabetes have changed in the past few years. The role of the liver and the important hormonal and enzymatic reactions are particularly stressed. The pathology and complications of the disease are described and attention directed to the phenomenon of insulin resistance. The peculiarities and proper treatment of infantile diabetes receive special attention. Dr. Mauriac

is an authority on diabetes and his book is not only interesting but practical.

THE FUNCTIONS OF THE LIVER. H. Benard and A. Gajdos. Masson et Cie, Paris, France, 1952, 5000 francs.

This volume constitutes, first of all, a critical description of our actual knowledge of liver functions. Modern biochemical research has altered many of the former classical conceptions of this great organ, and thus influenced our ideas of pathology and treatment. The personal opinions and views of the authors are concisely presented, not infrequently differing in some respects from average viewpoints. The book selects those pathological and functional facts which will be of value in helping to clarify the complex evolution of our knowledge of hepatic diseases.

GASTROINTESTINAL X-RAY DIAGNOSIS. Max Ritvo, M.D. and I. A. Shauffer, M.D., Lea & Febiger, Philadelphia, $20.00.

This beautiful book of 839 pages is devoted to diagnostic x-ray procedures in conditions of the gastrointestinal tract. Where clinical findings are necessary, they are presented. Separate chapters are devoted to the pharynx and esophagus; stomach; duodenum; jejunum and ileum; colon; appendix; gallbladder and liver; pancreas, spleen, mesentery, omentum, peritoneum and abdomen; and to hernias. The material is largely from the files of the Boston City Hospital. The book represents an experience of 30 years devoted to roentgenology. There are 470 illustrations, 2 in color. The book should be used by everyone interested in gastroenterology.

GENERAL ABSTRACTS OF CURRENT LITERATURE

WILDHIRT, DR. EGMONT: *Therapy of Acute, Severe Liver Damage.* Mediz. Welt. 20, 29, 941, July 1951.

A new type of treatment has been successfully tried in thirty cases of viral hepatitis, of a very severe nature. Of the thirty cases six were in deep coma when therapy was started, fifteen were in precoma, and the rest gave every indication that they would follow the same course. Twenty-one cases had a serum bilirubin of more than 15 mg%. Fourteen cases were also followed by peritoneoscopy and liver biopsy, and the diagnosis of acute necrosis of the liver was confirmed. The treatment consisted of a continuous intravenous drip infusion of Laevocholin* and Pancortex**. Laevocholin is a special preparation of fructose and cholin for intravenous use. Pancortex is an aequeous extract of the whole adrenal cortex. These preparations were given in sterile Ringer's Solution. A total daily dose of 20-30 gm of fructose, 4-6 gm of cholin and 5-10 cc Pancortex were administered in such fashion.

The results of the therapy were as follows: three of the six patients in coma died. Their condition had too far advanced to hope for a better result. The other three lived. One of the cases slumped twice into deep coma, but finally recovered and left the hospital in good condition. A peritoneoscopy was performed on him and it was estimated that approximately 2/3 to 3/4 of the liver had become necrotic. All other cases took a favourable course. Only one case possibly will develop a cirrhosis. He is being checked with liver biopsies. It is noteworthy that under the treatment schedule as outlined not a single severe case went into coma.

The following considerations led to the adoption of the therapy presented. Fructose is a specially liver active carbohydrate. According to the investigations of Gremels and Cori the affinity of fructose to the liver, even to the damaged liver, exceeds that of glucose threefold. Cholin is added although its exact position and mode of action in the therapy of liver diseases is still unsolved. It is certainly a lipotropic agent which may affect the fatty metamorphosis which has to be considered an expression of the severe toxic damage of the liver. It seems that cholin has also a secondary detoxifying role. Lang could demonstrate that cholin can replace methionin as a lipotropic agent and free methionin for its detoxifying action. We choose an aequeous extract of the adrenal cortex because it contains sufficient gluco-corticoids to influence the carbohydrate metabolism favourably. For the same reason we advise against the use of synthetic adrenal-cortical preparations because they consist almost exclusively of mineral-corticoids, having essentially no influence on the carbohydrate metabolism. In addition, they may disturb the salt metabolism which is already seriously altered in cases of hepatitis. Using mineral-corticoids in cases of acute hepatitis Kalk observed elevation of blood pressure, retention of non-protein nitrogen, development of edema, in short a real hepato-renal syndrome.

In summary the use of intravenous infusion of Laevocholin and Pancortex in cases of severe acute hepatitis has given excellent results in our hands and we consider it the best therapy presently available.

Egmont Wildhirt, Kassel, Germany.

*Laevocholin supplied by Deutsche Laevosan-Gesellschaft, Mannheim.

**Pancortex supplied by Dr. Georg Henning-G. m. b. H. Berlin-Hamburg.

SPIRA, LEO: *Tetanoid symptoms in chronic fluoric poisoning.* Deutsche Med. Wo. 76, 49. Dec. 7, 1951.

Protracted ingestion of toxic amounts of fluorine has been clinically found to produce a disease picture affecting the following organ systems: (1) The gastrointestinal tract. There is obstinate constipation and flatulence, sometimes associated with attacks of severe colicky pain. (2) The peripheral nervous system. There are paresthesiae affecting mainly the area supplied by the dorsal cutaneous branch of the ulnar nerve. Pruritus, even without any visible dermal changes, and attacks of cramps in the calves are frequently encountered. (3) Organs biologically originating in the ectoderm and regulated by the parathyroid glands, viz: the skin and its appendages, the teeth, nails and hair. Outstanding amongst the dermatoses are cheiro-

pompholyx, "dhobie-itch," urticaria, furunculosis and infantile eczema. The teeth present a mottled appearance, if toxic amounts of fluorine were ingested during the first 8 years of life, i.e. before the calcification was completed. Similar changes occur in the nails ("mottled nails"), and the hair falls out prematurely.

The disease picture of chronic fluorine poisoning is similar to that of latent tetany or "idiopathic" hypoparathyroidism, and responds favourably to antitetanic treatment.

In an endeavour to reproduce the disease in rats, gradually increasing doses of NaF were added to the drinking water over a long period of time. This resulted, apart from mottling of the teeth, in severe dermal changes and pronounced alopecia. On interruption of the experiment, and on substituting distilled for the fluoridated drinking water and addition of calcium carbonate to the food, there was a prompt retrogression of the lesions. Resumption of the experiment in the same animals brought about a recurrence of the condition, but reintroduction of the treatment described led once more to its complete disappearance.

Fluorine is a nerve toxin affecting mainly the vegetative nervous system. Its deleterious action consists in its ability to precipitate the calcium salts stored in the body as a material indispensable for sustaining the vitality of most of the organic functions. It also appears to interfere with the mechanism of the action of vitamin B.

Albot, G., Toulet, J. and Bonnet, G. F.: *Tests in Front and Side-view Cholecystography.* Arch. Mal. App. Dig., T. 40., No. 11. Nov. 1951, pp. 1187-1193.

The authors have striven to draw more accurate conclusions from the study of the contraction of the gall-bladder in the diagnosis of dyskinesia.

Recorded tests by cholecystography using numerous exposures as well as pharmaco-dynamic substances administered after or at the same time as the Boyden meal, have furnished information theoretically interesting but of no great practical value.

On the other hand, the authors consider that side-view exposures are essential both before and after the Boyden meal. Actually this incidence enables them to form a more exact idea of the morphology and to discover in a much more accurate way the contraction of the gall-bladder and its pathological variations.

Furthermore, they emphasize the importance of dorsal decubitus, in contrast to the more usually adopted procubitus.

Finally, the exact estimate of the gall-bladder's projection surfaces, front and side-view, thanks to the use of tracing paper marked off in millimeters, enables them to estimate exactly, with figures, the rate of evacuation of the gall-bladder.

It is thus possible by this method, to distinguish between two phenomena up till now confused in ordinary cholecystography: on the one hand the effort of vesicular contraction, and on the other, the action of its evacuation.

The effort of contraction after Boyden's meal is seen in front-view as a raising of the gall-bladder under the edge of the ribs and as a recoil of the spine. But it is especially easy to determine from the side-view by a straightening up of the lower part of the gall-bladder. The large axis of the gall-bladder in profile after Boyden's meal makes a more marked angle with the spine, and this difference in the angle is a sure sign of the contraction of the gall-bladder.

Other indications of contraction may moreover be shown up on the side-views; for example, a retraction of the entire shadow of the gall-bladder, a roof-shaped angle due to the more marked retraction of the infundibulum, or a mere arc-shaped contraction due to the change in direction of the posterior curve of the shadow of the gall-bladder.

All these signs enable the contraction of the gall-bladder to be affirmed and its intensity to be determined.

Furthermore, the taking of front and side exposures both before and after Boyden's meal enables the volume of the gall-bladder to be calculated easily and consequently exact figures of the evacuation of the gall-bladder to be given.

With the help of these two facts, one is able to distinguish between:

—normal gall-bladders with normal contraction effort (the angle increases 10 degrees), and the action of normal evacuation (60 to 65% in the case of a woman one hour after Boyden's meal).

—cystic or infundibulo-cystic hypertension with a normal or excessive contraction effort.

—hyperkinetic or irritable gall-bladders with very strong contraction and excessive evacuation.

—finally, vesicular hypotension or atony with very slight evacuation, but proportionate to the effort of contraction which is likewise very slight.

In conclusion, the authors advocate the taking of 5 exposures as a standard cholecystographic technique: the first in a standing position with compression and the others from the front and side, before, and one hour (in the case of a woman) or one and a half hours (in the case of a man) after Boyden's meal. These last four exposures should be taken in dorsal decubitus with a bulb above for the front view exposures, and a bulb on the left of the patient for side view exposures.

Hirsch, W. and Muench, O.: *Roentgenological diagnosis of the duodenum inversum.* Fortschr. Geb. Roentgenstrahlen 75, 4, 445. Oct. 1951.

After a genetic definition of the conception "duodenum inversum" a review of the literature and a series of own cases is presented. It is stated that from a genetic point of view these cases cannot be called as real duodenum inversum. They are generally anomalies conditioned by incomplete rotation of the duodenum or by changes of the position of the organs following gastroptosis or kyphoscoliosis in a duodenum mobile. To this collection of cases is added one case, in which the diagnosis of partial inversion of the duodenum is genetically and roentgenologically justified, as it meets the criteria, which must be present in a critical study of a duodenal inversion.

Franz J. Lust.

SENTURIA, HYMAN R. AND HEIFETZ, CARL J.: *The roentgen appearance of intestinal pouches following lateral anastomosis.* Am. J. Roentg. 67, 2, 227, February, 1952.

Attention is directed to the roentgenologic appearance of blind pouches following lateral intestinal anastomoses. Six cases in which blind pouches were demonstrated roentgenologically are recorded. Five of these occurred in the small intestine and one in the large intestine. Three of the patients had symptoms directly attributable to the presence of the pouch. Obscure gastrointestinal symptoms such as colicky abdominal pain, distention, nausea, and vomiting may be explained by the roentgen demonstration of a blind intestinal pouch. Macrocytic anemia may also be caused by this abnormality. Attention may be directed to the pouches by barium retained within them after evacuation of a barium enema or during barium studies on the small intestine. Unwarranted surgery can be avoided or curative surgery can be performed if the correct interpretation of the roentgen findings is made.

Franz J. Lust.

NORMAN, OLAF.: *Studies on hepatic ducts in cholangiography.* Acta Rad. Suppl. 84, Stockholm, 1951.

Norman decribes the technique of cholangiography as practised at the University Clinics of Lund. Satisfactory operative cholangiography requires a full capacity x-ray equipment to permit short time exposure; the use of water soluble contrast media; cholangiograms from different angles at every examination. The latter provision is important to obtain views without superimposition of the different hepatic branches. The intimate teamwork of anesthetist, roentgenologist and surgeon is stressed. No cholangiograms should be taken during the injection of the contrast medium, because the injection is liable to dislodge stones, which may then float about and thereby escape visualization. Primary cholangiography before choledochotomy and control examination after choledochotomy are necessary. Postoperative examination through an indwelling tube is of importance.

Norman reports 46 cases of hepatic calculi, in 31 of which stones were visualized in the intrahepatic ducts. The knowledge of the roentgen anatomy of the hepatic tree is stressed, especially the different anomalies are described. As in the choledochus, the stones in the hepatic ducts will be directly outlined in the cholangiograms. The presence of a stone might also be deduced from an incomplete filling of a branch, even though the stone itself is not visualized. Comparison of the roentgen findings and the operative findings showed that in 20 cases all the stones were removed but that in 26 some stones had been left in spite of choledochotomy.

The paper is very well illustrated, with an extensive bibliography, written in English. It can be recommended to all those interested in this subject.

Franz J. Lust.

TODD, J. W.: *Simple gastric ulcer with achlorhydria.* Brit. Med. J., Dec. 29, 1951, 1565.

Todd reports a woman who showed achlorhydria after histamine injection and yet had two simple peptic ulcers of the stomach revealed at operation. They were not malignant. Two years previously she had had ulcer symptoms (which responded to treatment) and achlorhydria on gastric analysis without histamine. Todd therefore feels that simple peptic ulcer can occur in a stomach which secretes no free acid. He refers to Walter Palmer's opinion that chronic gastric ulcer does occur in patients with *transitory* achlorhydria but not in complete and permanent achlorhydria. Todd's case may possibly furnish an exception to Palmer's rule.

WILLNER, C. E. and PERLOW, S.: *Observations in acute peptic ulcer perforations.* Illinois Med. J., 101, 4, April 1952, 203-208.

A review of 76 cases of acute perforation of peptic ulcer indicates that the most favorable type of therapy in this group of cases was early surgical closure of the perforation under spinal anesthesia with liberal use of antibiotics. The antibiotic agents have been almost single-handedly responsible for the improvement in mortality.

HUGHES, E. S. R. AND SHAW, H. M.: *Acute diverticulitis of the colon with peritonitis.* Med. J. Australia, Feb. 23, 1952, 259-260.

Peritonitis caused by diverticulitis is an uncommon surgical emergency. Before the introduction of penicillin, the best results followed laparotomy and drainage combined with colostomy. In recent years, the combination of penicillin and other modern antibiotics has rendered colostomy unnecessary. Seven of their 25 patients who were treated by laparotomy and drainage had the advantage of penicillin therapy. Six of them recovered, the other dying of bronchopneumonia two days after operation.

THOMAS, M. E. H.: *"Epidemic" abdominal colic associated with steatorrhea.* Brit. Med. J., March 29, 1952, 691-692.

Some 25 cases in a day nursery were affected by a disease characterized by abdominal cramps, vomiting and fatty stools. The attack lasted only 4 days, with occasional relapses. The disease appeared highly communicable, as some members of the staff became ill, though not showing diarrhea, vomiting or fatty stools. Careful bacteriological examination of the stools failed to reveal a possible pathogen. Although the stools were fatty, the urine contained no bile. It appears that fat absorption was interfered with in the small gut. A virus might conceivably be responsible. This may be a new disease and further cases should be looked for.

HARVILL, T. H.: *Amebiases: a common clinical problem.* Texas State J. Med., 48, 1, Jan. 1952, 24-27.

Infestation with E. histolytica is more frequently productive of vague constitutional symptoms and gastrointestinal complaints; acute dysentery is the exception rather than the rule. The irritable colon syndrome typifies the complaints often encountered—gas, irregular movements, and mucus. There is lassitude, fatigue, irritability, and capricious appetite. The only abnormal laboratory finding is the presence of the parasite in the stool. An enlarged liver, not due to am-

ebic hepatitis, may be present, but subside on specific treatment. There are not too many pathologists who excel at stool examination.

Emetine, so useful in acute dysentery, has no place in chronic, low grade colonic amebiasis. The author likes vioform (250 mg. every 3 or 4 hours for 10 to 14 days).

KENNEDY, T. L.: *Gastric carcinoma and acute perforation.* Brit. Med. J., Dec. 22, 1951, 1489-1492.

Of a total of 11 acute perforations in 5 years, 6 proved to be cancerous. The incidence of carcinoma in perforated gastric ulcer was at least 16.7 percent. The surgeon should consider the possibility of malignancy in every perforated ulcer. Simple suture of the ulcer, followed by gastrectomy after 2 or 3 weeks is recommended. The incidence of cancer in prepyloric perforations is so high (20 percent) that secondary gastrectomy is advised in all patients over 40 years of age.

GILMOUR, D. AND SYKES, A. J.: *Westergren and Wintrobe methods of estimating E. S. R. compared.* Brit. Med. J., Dec. 22, 1951, 1496-1497.

The Wintrobe method using oxalates, and the Westergren method using sodium citrate as anti coagulant were compared. On the whole the Westergren method gave higher readings than the Wintrobe and seemed to be more sensitive. The authors thought that in a few cases the Wintrobe method was misleading.

STEWART, I. S. AND THOMSON, G. R.: *Argentaffin tumor of the ileum with perforation.* Brit. Med. J., Dec. 1, 1951, 1316-1318.

A case of perforation of the small intestine, in a woman aged 40, is reported. The perforation occurred in one of three argentaffin tumors of the ileum. Treatment was by excision of all three, restoration of continuity of the gut, closure of the abdomen without drainage after liberal application of sulphanilamide powder to the operation sites. The patient recovered uneventfully.

BOUCOT, K. R., DILLON, E. S., COOPER, D. A., MEIER, P. AND RICHARDSON, R.: *Tuberculosis among diabetics. (The Philadelphia survey)* Ann. Rev. Tuberculosis (Part 2), 65, 1, Jan. 1952.

The prevalence of tuberculosis was 8.4 percent among 3,106 Philadelphia diabetics surveyed in 1946. This was twice as high as the prevalence in a group of healthy industrial workers adjusted for age, race and sex. The diabetics younger than forty had a prevalence of active T. B. of 5.3 percent, as contrasted with 1.7 percent for those older than 40. The diabetics younger than 40 had a T. B. prevalence of 5 percent with diabetes of less than 10 years' duration, while the prevalence of T. B. was 17 percent when the diabetes had been present for more than 10 years. The prevalence of active T. B. increased from 1.5 percent for those who received no insulin or no more than 40 units to 5.3 percent for those who received more than 40 units daily. As in non-diabetics, T. B. was twice as common among those below standard weight as among those above standard weight. This should be considered in connection with the common custom of keeping diabetics below standard weight.

IDE, A. W.: *Intussusception.* Journal-Lancet, Dec. 1951, 541-550.

Intussusception is the most frequent cause of intestinal obstruction in infants, but when the picture of obstruction is present, the process already is far advanced. Perhaps the commonest cause of intussusception is a swelling of a Peyer's patch which stimulates peristalsis as a foreign body might. The mortality is greater the longer the condition has existed prior to operation. The classical symptoms of intussusception in infancy are colic, vomiting, palpable mass and melena. In the U. S. A. treatment is almost entirely surgical, but in Australia and Scandinavia good results have been achieved by rectal irrigation.

SMITH, B. K. AND ALBRIGHT, E. C.: *Carcinoma of the body and tail of the pancreas: report of 37 cases studied at the State of Wisconsin General Hospital from 1925-1950.* Ann. Int. Med., 36, 1, Jan. 1952, 90-98.

A marked predominance of males (84 percent) was found. The average age was 58.1 years. Duration of illness was 9.1 months. The correct diagnosis was made in only seven cases before laparotomy or autopsy, the common incorrect diagnosis being carcinoma of the colon. The commonest symptoms were abdominal pain, loss of weight, anemia, nausea, vomiting and constipation. Two findings which were unique, and which appeared with significant frequency were venous thrombi and abdominal pain related to position. Such pain, aggravated by lying down and relieved by the erect position, was noted in 43 percent. Ascites implies liver or peritoneal metastasis or portal vein thrombosis. Barium studies of the G. I. tract were usually negative.

GRAY, K. D.: *Xanthomatous biliary cirrhosis, with report of a case.* Med. J. Australia, Jan. 5, 1952, 6-8.

Gray reports a case showing liver enlargement, mild jaundice, a macrocytic anemia and an extremely high blood cholesterol. He improved greatly upon the use of a fat-free diet, low in cholesterol plus lipotropic agents and vitamin B_{12}. The sequence of events may have been as follows—chronic alcoholism leading to deficient intake of vitamin B complex and proteins, which in turn caused liver damage resulting in obstructive jaundice, hypercholesterolemia and macrocytic anemia. Although the skin has not as yet shown any xanthomatous lesions, Gray feels the case should be classified as xanthomatous biliary cirrhosis as described by Thannhauser and Magendantz in 1937. Furthermore, while the blood cholesterol reached 12 times its normal concentration, the serum was definitely milky in contradistinction to the postulate of the Boston authors that the serum should be transparent. The obstructive jaundice is produced presumably by xanthomatous lesions in liver ducts.

O'BRIEN, J. R.: *Multiple argentaffinomata of ileum revealed by secondary growth in the epididymis.* Brit. Med. J., Dec. 1, 1315-1316.

A case is reported of a man of 73 whose right testicle was removed because it was abnormal during a repair of a hernia. On examination the epididymis contained several carcinoid tumors. (Cope in 1930 gave the only

record of a secondary growth in the testis, eight years after resection of a part of the small gut which contained a single annular primary growth). Apparently on the strength of this example, and in the presence of a normal G. I. barium series, the patient was operated upon, and the terminal 3 feet of ileum was found to be studded with about 60 white plaques, varying in size from 0.2 to 2 c.m. in diameter, distributed at random beneath the serosa. The large plaques were producing marked stenosis of the intestine. This section of the ileum was removed as well as a large plaque in the mesentery and secondary deposits were felt in the liver. The patient improved greatly for 2 years but died 3 years after the operation with "myocardial degeneration due to secondary carcinoma" with "generalized edema of the limbs."

ZAVALA, D. C. AND HAMILTON, H. E.: *The recognition and treatment of hepatic amebiasis.* Ann. Int. Med., 36, 1, Jan. 1952, 110-125.

The authors report 7 cases of hepatic amebiasis. Helpful diagnostic hints—(1) tender and often enlarged liver, (2) "fading suntan" complexion of the skin, (3) elevation or fixation of the right leaf of the diaphragm, (4) little or no change in liver function tests, (5) positive complement fixation test, with a fall in titer following specific amebicidal therapy and (6) specific therapeutic response. Chloroquine and emetine are both specific for amebic hepatitis and abscess, chloroquine being the drug of choice. Chloroquine should always be given in combination with one of the local amebicidal drugs, preferably diodoquin.

LONGWORTH, T. I.: *Congenital megacolon.* Arch. Pediat., 68, 10, Oct. 1951, 467-472.

A long case report of an instance of congenital megacolon is presented, with poor results from medical management, and equally poor results from a sympathectomy. Finally, Swenson's operation was performed with good results. There is a distal constricted portion of bowel in which the constriction is due to an absence of nerve ganglia of the intramural plexus. The dilated gut proximal to this portion is histologically normal. Swenson resects the rectum and rectosigmoid with preservation of the sphincters.

ARDEN, F.: *Rupture of the liver in the newborn.* Med. J. Australia, Nov. 10, 1951, 632-635.

Six cases of rupture of the liver in the newborn with intraperitoneal hemorrhage are reported with four recoveries. The condition is not particularly rare. Successful treatment depends on early diagnosis and immediate blood transfusion. Usually the diagnosis is made at autopsy, but the symptoms of pallor, weakness and pulselessness coming on about 60 hours after birth, especially in post-mature, oversized infants with dullness in the right flank gradually proceeding to the left flank, should make an early diagnosis possible. Apparently the hemoglobin usually falls to 50 percent or slightly less, at the time of collapse.

BARDEN, R. P.: *Pre-malignant lesions of the gastro-intestinal tract. I. The significance of roentgenologic evidence of hypertrophic gastritis.* Am. J. Roentgen. and Rad. Ther., 66, 6, Dec. 1951, 915-921.

Barden presents 6 cases with reproductions of gastric films which definitely show the ease with which hypertrophic gastritis can be radiologically confused with advanced carcinoma. An unpredictable number of patients with hypertrophic gastritis of several years' duration will develop cancer. Hence prophylactic gastrectomy should be considered in all patients with this pre-malignant lesion.

GILLESPIE, J. B. AND BLISS, H. E.: *Peptic ulcer in childhood.* Arch. Ped. 68, 8, Aug. 1951, 361-72.

The authors present 5 cases of duodenal ulcer and one of gastric ulcer in childhood. In all cases the diagnoses were confirmed by x-ray studies. The ages varied from two to nine years and in 2 cases the lesions and symptoms persisted into young adult life. The presence of ulcer should always be suspected in any child with vague or ulcer-like symptoms. Pain, vomiting and constipation are the most frequently observed symptoms of peptic ulcer in childhood. Relief by milk or alkali was noted in several cases. In one case it is possible that the use of aureomycin for a respiratory infection initiated or aggravated the ulcer. Sometimes a gastric pyloric ulcer may simulate hypertrophic pyloric stenosis in infants of nine weeks of age, as recently reported. The ulcers of childhood are so persistent or recurrent as to suggest that adult ulcer may have its beginnings in childhood. The three x-ray pictures reproduced are convincing evidence of the presence of ulcer.

HOLMES, J. H. AND PERCEFULL, S. C.: *Liver function studies during cortisone therapy.* Ann. Int. Med., 35, 3, Sept. 1951, 608-14.

In 25 patients receiving cortisone treatment (the majority for rheumatoid arthritis), complete studies of liver function indicated that cortisone did not produce any significant changes in the various tests. Minimal changes were found, however, in the thymol turbidity, serum cholesterol, cholesterol-ester ratio and serum esterase. Changes in the thymol turbidity might be explained by alterations in the electrophoretic pattern. As regards serum cholesterol, Adlersberg, et al recently found an average increase of 15 percent in the total serum cholesterol, which compares with the present authors' average maximum increase of 10 percent. Further, the authors found in giving cortisone to 2 cases of hepatic disease that liver function was in no way impaired.

SPECIAL CARE FOOD PACKAGES FOR HOLIDAY GIFTS OVERSEAS

Americans who wish to assure Thanksgiving and Christmas cheer for relatives, friends or needy families overseas can take their choice this year of three CARE food packages especially prepared for gift-giving.

The annual CARE Holiday Package, containing a whole canned turkey plus the dinner trimmings for as many as 12 persons, is again available at $18.75 for delivery in Austria, Belgium, Finland, France, West Germany and Berlin, Great Britain (England, Scotland, Wales and Northern Ireland), Greece, Italy, the Netherlands and Norway.

In addition, CARE offers the canned turkey alone at a cost of $12, and a tasty $6.95 Budget Food Package designed to supplement the bird or travel proudly on its own. These two assortments may be ordered for recipients in East Germany and Yugoslavia as well as the above countries, while the Turkey Package is also available for Japan, Okinawa and the Philippines.

Orders may be mailed to CARE, 20 Broad St., New York 5, N. Y., or any local office of the non-profit agency. Deadline for Thanksgiving orders is November 1; for Christmas delivery, December 1.

All of the CARE turkeys are full-meated Beltsville Whites, each weighing at least 8 and 1/3 pounds. Steam-roasted in their own juices and packed in two pounds of lard, they can be served hot or cold.

Accompanying the bird in the CARE Holiday Package are: 1 lb. each of plum pudding, bacon, coffee (or tea), chocolate candy, hard candy; 29 oz. peaches; 15 oz. raisins; a half-pound of butter and 1¼ oz. mustard.

Contents of the special CARE Budget Food Package include: 2 lbs. each of bacon, sugar, rice; 1 lb. each of coffee (tea for Great Britain), butter, preserves, candy (assorted chocolates and hard candies); 15 oz. raisins and 12 oz. luncheon meat.

BREON OFFERS HIGH POTENCY INJECTABLE B-COMPLEX PRODUCT

George A. Breon & Company has introduced a product described as supplying a high concentration of the principal components of the Vitamin B-Complex.

The product, used for parenteral injection, is called Breonex-M. It is indicated especially when there is need for high potency, greater certainty of absorption, or rapid improvement of acute conditions of B-complex deficiency. The firm notes that administration of Breonex-M may be desirable in the presence of inadequate dietary intake, increased metabolism occurring in prolonged fever and hyperthyroidism, and particularly when absorption or utilization is impaired by gastro-intestinal dysfunction.

Breonex-M is recommended as a companion product to Breonex-L, a potent Vitamin-B complex injectable. The new preparation is offered in response to the requests of the medical profession for a larger multiple dose vial.

A 30 cc. vial of diluent is supplied with the larger vial which permits the doctor to prepare one of two types of dilutions.

Breonex-M is supplied in combination packages, each 10 cc. vial accompanied by 30 cc. of aqueous diluent.

MEDICAL FIRM APPOINTS MID-WEST SALES OFFICIAL

New York, N. Y.—Robert S. Bunning has been appointed assistant regional sales manager for the mid-western states of George A. Breon & Company, pharmaceutical manufacturer, it was announced by Frederick O. S. Spencer, vice-president in charge of sales.

Mr. Bunning has been associated with the concern since 1946. Prior to his present assignment he represented Breon in the eastern part of North Carolina, from headquarters in Raleigh. He now assumes broader responsibilities as assistant to Clyde A. Johnson, regional sales manager, who directs mid-west sales activities from the firm's branch offices in Chicago.

Mr. Bunning will be stationed in Des Moines, Iowa, and will represent Breon in Montana, Colorado, South Dakota, Nebraska, Iowa, Kansas and Missouri. He received a Bachelor of Science degree from the University of Pennsylvania, where he remained to continue graduate studies in economics.

Breon manufactures an extensive line of injectable medicinal products, including Acorto-Gel, an ACTH preparation, which the firm distributes directly to the medical profession. It also supplies hospitals, and the retail and wholesale drug trade.

BECTON, DICKINSON AND COMPANY APPOINTS L. W. FROHLICH ADVERTISING AGENCY

Mr. D. Wayne Johnson, Vice President for Sales of Becton, Dickinson and Company, Rutherford, N. J., has announced the appointment of L. W. Frohlich & Company, 56 East 52nd St., N. Y. C., as advertising agency for the company effective September 1, 1952. Becton, Dickinson and Company manufactures many well-known surgical and medical specialties: including B-D Hypodermic syringes and needles, B-D fever thermometers, and the ACE (R) line of rubber elastic bandages and men's and women's seamless elastic hosiery.

Advertising plans include special campaigns on each of these lines. Professional, trade and national media will be used. Plans are currently underway for introducing a new B-D development: the first seamless full-footed elastic hosiery for men which will not require the wearing of overhose.

POTENT PROTEIN HORMONE INTRODUCED BY BREON

Chorionic gonadotropin, a hormonal substance obtained from human pregnancy urine, has been introduced to the medical profession in a desiccated powder with accompanying diluent, by George A. Breon & Company, under the trade name of Riogon.

The Breon product, a water soluble buffered gonadotropic substance, is a glycoprotein and is standardized in international units. One international unit is equivalent in gonadotropic activity to 0.1 mg. of the standard preparation.

In making the protein hormone available, the firm indicates that it has a high potency. For intramuscular use only, Riogon is used in the treatment of cryptorchism, functional uterine bleeding, and has proven beneficial in some cases of common acne. Its chief application

announcing the Wyeth peptic ulcer service

Wyeth — long conceded the leader in peptic ulcer medication—now offers you a comprehensive peptic ulcer service. This service will help you give your peptic ulcer patients the latest and most widely accepted therapy with a minimum expenditure of your time and effort.

the complete peptic ulcer service

---

for your patients

what you should know about healing your ulcer — booklet — by staff members of the New York Hospital—Cornell Medical Center. Tells your patient all he need know about his ulcer. Saves you time and effort in psychiatric and medical management of the ulcer patient.

peptic ulcer diet sheets—simple, definite instructions for the diet of the peptic ulcer patient.

for the medical profession only

peptic ulcer—film—1 reel, 16 mm., color and sound; thirty minute presentation by staff members of the Lahey Clinic; covers uncomplicated cases. For group showing.

special problems in peptic ulcer—film—1 reel, 16 mm., color and sound; thirty minute presentation by staff members of the Lahey Clinic. For group showing.

peptic ulcer—booklet—a guide to diagnosis and treatment; based on film.

special problems in peptic ulcer—booklet—a handbook on diagnosis and treatment; from the film.

basic physiologic facts which account for the continued acceptance of Amphojel—booklet—a discussion of peptic ulcer and its management, originally printed for Wyeth representatives but widely read by physicians.

Wyeth peptic ulcer medication

Amphojel®, N.N.R. (Aluminum Hydroxide Gel, Alumina Gel)—For the medical management of gastric and duodenal ulcer; or for the control of symptomatic gastric hyperacidity.

Amphojel without Flavor, N.N.R.

Amphojel with Mineral Oil.

Amphojel, Tablets, N.N.R. (Dried Aluminum Hydroxide Gel, Hydrated Alumina Tablets), 0.3 Gm. (5 grains); 0.6 Gm. (10 grains).

A-M-T® Suspension—formerly Amphojel w/ Magnesium Trisilicate.

A-M-T Tablets, (Alumina-Magnesium Trisilicate Tablets).

Phosphaljel®, N.N.R. (Aluminum Phosphate Gel)—For marginal ulcer.

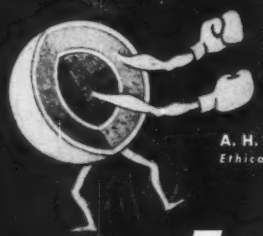
Sebella®, Tablets (Aluminum Hydroxide with Belladonna and Phenobarbital)—Antacid therapy with effective spasmolysis and mild sedation.

Wyeth

THE *two-fisted* TABLET

for the dyspeptic patient

Entozyme 'Robins' is indicated for the many varied manifestations of functional dyspepsia, so often accompanied by enzymatic hypofunction:



- releases *pepsin* in the stomach
- releases *pancreatin* and *bile salts* in the small intestine.

A. H. ROBINS CO., INC. · Richmond 20, Va.
Ethical Pharmaceuticals of Merit since 1878

Entozyme Robins

FORMULA: Each double-layered tablet contains pepsin N.F. 250 mg., pancreatin U.S.P. 300 mg., and bile salts 150 mg.

"...and don't forget the VITAMINS!"

Peptic ulcer often interferes with the ingestion of a balanced diet, and the period of tissue repair further increases vitamin requirements. Established therapy, including restrictive diets and antacids, also must consider the problem of vitamin intake and absorption. A balanced vitamin preparation is a dependable means of assuring adequate intake of the essential nutritional factors.

MERCK & CO., INC., RAHWAY, N. J.—as a major manufacturer of Vitamins—serves the Medical Profession through the Pharmaceutical Industry

Meat...

and Its Important Contribution of Essential Amino Acids

Although the daily allowance of protein recommended for human beings has been established for some time,[1] only very recently has a recommended daily intake of individual essential amino acids been proposed.[2] These new criteria now give a more accurate means for nutritionally evaluating the protein contribution of meat than was possible just on the basis of the gross amount of protein meat provides.

The table which follows gives the proportions of the recommended daily intake of individual essential amino acids provided by six ounces of cooked meat, the approximate average per capita daily consumption in the American diet. Note that though furnishing about 52 per cent of the daily protein allowance for a normal adult male, six ounces of meat supplies more than the recommended daily intake for a majority of the essential amino acids and a goodly proportion of the recommended intake of the remainder.

Percentages of Recommended Daily Intake of Eight Essential Amino Acids and of Protein Contributed by 6 Oz. of Cooked Meat*

Essential Amino Acids	Beef[3]	Lamb[4]	Pork[4]
L-Isoleucine	141	121	127
L-Leucine	150	120	125
L-Lysine	202	163	172
L-Methionine	42	34	40
L-Phenylalanine	70	63	70
L-Threonine	160	169	183
L-Tryptophan	90	90	100
L-Valine	136	107	113
Protein	56	49	51

*In the calculations, averages of the percentages of protein in six different cuts of each type of cooked meat were used, as were averages of the percentages of the amino acids in the protein of the respective cuts.

Every kind and cut of meat is not only an excellent source of the essential amino acids but also of the nonessential amino acids, the B group of vitamins, iron, and other essential minerals. Morever, meat is rapidly and almost completely digested, has a stimulating influence upon appetite and digestion, and gives a gratifying sense of satiety. All these nutritional and physiologic advantages of meat fully justify its prominent place in normal diets of persons of all ages and in many special diets.

REFERENCES

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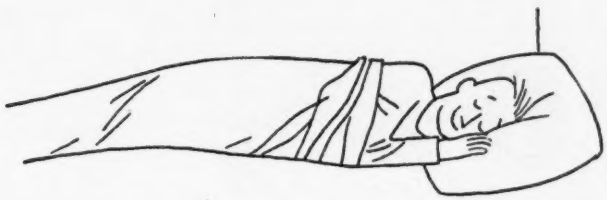
3. Greenwood, D. A.; Kraybill, H. R., and Schweigert, B. S.: Amino Acid Composition of Fresh and Cooked Beef Cuts, J. Biol. Chem. *193*:23 (Nov.) 1951.
4. Schweigert, B. S.; Guthneck, B. T.; Kraybill, H. R., and Greenwood, D. A.: The Amino Acid Composition of Pork and Lamb Cuts, J. Biol. Chem. *180*:1077 (Oct.) 1949.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute

Main Office, Chicago...Members Throughout the United States

GIVE PROMPT RELIEF FROM CONSTIPATION WITH SAL HEPATICA®



Patients want prompt relief from constipation. Provide it with antacid SAL HEPATICA. There is no laxative lag when SAL HEPATICA is used.

RESTFUL SLEEP is not impaired when laxation occurs before bedtime. Assure this by recommending that SAL HEPATICA be taken one-half hour before dinner.

ACTIVE DAYS, free from the discomforts of constipation, are possible if SAL HEPATICA is taken one-half hour before breakfast. Laxation usually occurs within the hour.

THE GASTRIC HYPERACIDITY which frequently is concomitant with constipation is relieved by this antacid saline laxative.

GENTLE ACTION, freedom from abdominal griping, may be obtained by regulation of dosage.

EFFERVESCENT, PLEASANT-TASTING, SAL HEPATICA is acceptable to patients.

BRISTOL-MYERS COMPANY, 19 WEST 50 STREET, NEW YORK 20, N. Y.

to the male is in cryptorchism. For this condition, treatment should not be continued after eight weeks in the absence of progressive testicular descent.

When other therapy has failed in functional uterine bleeding, Breon observes that Riogon may bring a return of the normal cyclic rhythm with ovulation. Intramuscular injections of 500 I. U. are given daily on the 15th day after the onset of bleeding and continued until the 25th day. To halt excessive uterine bleeding, 500-1,000 I. U. are given daily, intramuscularly, until the hemorrhage has been controlled.

In acne vulgaris, an injection of 500 I. U. once a week will generally modify the hyperfunction of the sebaceous gland, the company states. After marked improvement, an injection of 1,000 I. U. per month at the time of ovulation is usually adequate for treating female patients. Weekly doses for the male are given up to several months, or until a favorable response is observed.

Riogon is supplied in combination packages, each vial being accompanied by 10 cc. of aqueous diluent. It is available in potencies of 5,000 and 10,000 units per 10 cc. vial.

PARKE, DAVIS & COMPANY PROMOTES A. D. MACPHAIL TO FIELD MANAGER IN WALKERVILLE BRANCH

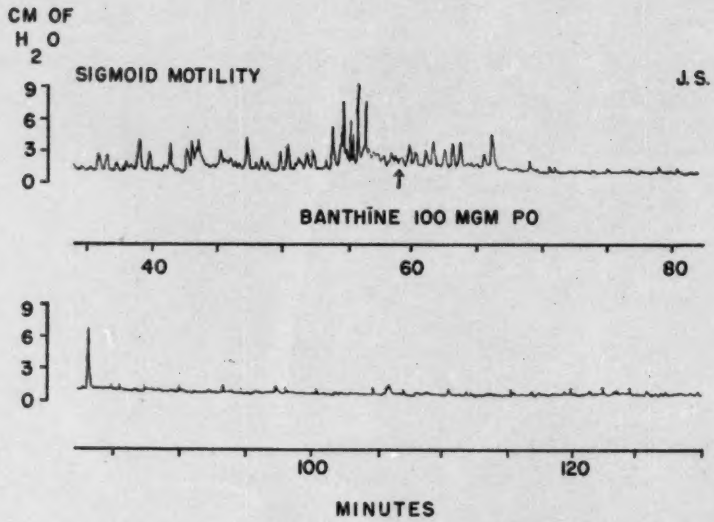
Windsor, Ont.—A. D. MacPhail has been appointed a field manager in the Walkerville branch of Parke, Davis & Company, Ltd., Graydon L. Walker, director of U. S. and Canadian sales, announced recently.

MacPhail will supervise sales territories throughout the province of Ontario in his new position, Walker said. He will serve under the direction of L. M. Budd, manager, Walkerville sales branch.

Born in Alvinston, Ont., and a graduate of the Ontario College of Pharmacy, MacPhail joined Parke-Davis in 1940. He was assigned as a sales and medical service representative with headquarters in Kingston, Ont., and later in Toronto.

After service during World War II in the Canadian Army, MacPhail returned to his Toronto territory, the position he has held until his present appointment.

INDEX TO ADVERTISERS



The effect of 100 mg. of Banthine on sigmoid motility. The contractions did not return during the experimental period.[1]

In Intestinal Hypermotility—Banthine®

"...has a prolonged inhibitory effect on human gastrointestinal motility....
The duration of its action is striking,...."[1]

It has also been observed that definite retardation in gastrointestinal transit time in individuals with hypermotility was attributable to the therapeutic effect of Banthine.[2]

BANTHINE® Bromide (brand of methantheline bromide)—a true anticholinergic—is available for oral and parenteral use.

1. Kern, F., Jr.; Almy, T. P., and Stolk, N. J.: Effects of Certain Antispasmodic Drugs on the Intact Human Colon, with Special Reference to Banthine (β-Diethylaminoethyl Xanthene-9-Carboxylate Methobromide), Am. J. Med. *11*:67 (July) 1951.

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RESEARCH IN THE SERVICE OF MEDICINE **SEARLE**